Cystatin C based equation accurately estimates glomerular filtration rate in children with solid and central nervous system tumours. Enough evidence to change practice?

^{1,2*} Andrew J. Dodgshun MBChB, FRACP, ^{3,4,5} Cathy Quinlan MD, FRACP, ^{1,5} Michael J. Sullivan PhD, FRACP

¹ Children's Cancer Centre, Royal Children's Hospital, Melbourne, Victoria 3052, Australia

² Department of Paediatrics, University of Otago (Christchurch), Christchurch, New Zealand ³
Department of Nephrology, Royal Children's Hospital, Melbourne, Victoria 3052, Australia

⁴ Department of Paediatrics, University of Melbourne, Melbourne, Victoria, 3052, Australia

⁵ Murdoch Children's Research Institute, Melbourne, Victoria, 3052, Australia

Corresponding Author:

Dr Andrew Dodgshun MBChB FRACP, Children's Cancer Centre, Royal Children's Hospital, 50
Flemington Road, Parkville 3052, AUSTRALIA

Phone: +61 3 9345 5522

Fax: +61 3 9345 6524

ajdodgshun@gmail.com

Running title: Cystatin C in paediatric oncology

Abstract word count: 218

Text word count: 2483

Tables: 2

Figures: 3

Supplementary table: 1

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/pbc.26043](#).

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Conflict of Interest: None to declare

GFR	Glomerular filtration rate
CysC	Cystatin C
CNS	Central nervous system
CKiD	Chronic Kidney Disease in Children
PETIA	Particle-enhanced turbidometric immunoassay
PENIA	Particle-enhanced nephelometric immunoassay

Abstract

Background: Assessing the glomerular filtration rate (GFR) of paediatric patients receiving nephrotoxic chemotherapy is a vital element of clinical practice. Isotopically measured GFR is the gold standard in terms of accuracy but requires injection of tracer followed by several hours of blood tests. Estimation of GFR using creatinine is widely used but inaccurate and there is increasing concern regarding its usage for paediatric oncology patients. Cystatin C (CysC) based equations are increasingly used in other paediatric specialities to estimate GFR and their usefulness in paediatric oncology practice is becoming evident.

Methods: We assessed the renal function of children with solid tumours and CNS tumours receiving nephrotoxic chemotherapy over a 1 year period using paired CysC and isotopic GFR.

Results: 56 sets of measurements were reviewed with estimated GFR predicted using CysC based and creatinine based equations. The best performing equation was the “new CKiD” equation which estimated GFR within 30% of the measured GFR on 86% of occasions, outperforming the Schwartz equation. If estimated GFR using this equation was $>100\text{mL/min/1.73m}^2$ all values of measured GFR were normal at $>90\text{mL/min/1.73m}^2$, a category containing two thirds of all measurements.

Conclusions: The new CKiD equation predicts GFR in paediatric patients with cancer with more accuracy than creatinine based equations. When the estimated GFR is $>100\text{mL/min/1.73m}^2$, isotopic GFR can be safely omitted.

Keywords: Cystatin C; pediatric oncology; child; glomerular filtration rate

Introduction

Children with solid and central nervous system (CNS) tumours frequently receive nephrotoxic chemotherapy. Nephrotoxicity may be cumulative over several cycles of chemotherapy and

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measurements of glomerular and/or renal tubular function are often performed at several points in therapy to assess the need for dose modification.

There are a number of methodologies for monitoring glomerular filtration rate (GFR) in children receiving chemotherapy, the simplest of which is serum creatinine. While creatinine passes freely through the glomerulus, it is also actively secreted by proximal tubules at unpredictable rates. It is secreted at a higher rate where there is renal dysfunction, leading to an overestimate of GFR of between 10-40%. [1]

Moreover, inter-individual variation of creatinine is largely dependent on muscle mass which may vary greatly among children of similar weight and age, [2] despite GFR remaining largely stable with a mean of 104mL/min/1.73m² over the age of 2. [3] To address variability creatinine-based equations have been developed to estimate GFR, the most commonly used of which is the Schwartz equation. [4] This equation and its successive modifications have the advantage of being simple to calculate using determinants which are readily available on all patients.

In children with cancer, where muscle mass may vary more widely than other populations due to disease and treatment, the use of creatinine based equations risks overestimating the true GFR. This is supported by several recent publications showing creatinine-based equations do not accurately predict GFR in children with cancer. Bernhardt et al tested the original Schwartz equation, the modified Schwartz equation and the Counahan-Barratt equation against isotopic GFR measurement and found that none provided a reliable estimate of GFR. [5] 24 hour creatinine clearance is an alternative method of estimating GFR but is difficult and time consuming for families and may not be any more accurate than bedside equations. [6]

Cystatin C (CysC) is a promising substitute for serum creatinine. Its function is unknown but production is regulated by a single gene and is stable in all nucleated cells. [7] Its physical characteristics and steady production make it an attractive candidate for a surrogate marker of glomerular function.

Several equations incorporating CysC have been developed for children, some simply mathematically manipulating the CysC value while others incorporate creatinine, CysC combined with other parameters such as age or height. [8-11] The largest study evaluating the performance of CysC to estimate GFR in children included 349 children in the Chronic Kidney Disease in Children (CKiD) cohort. [9] The equation, named the "CKiD equation" estimated GFR within 30% of a measured GFR 87.7% of the time in children with chronic kidney disease. This study was updated in 2012 with a total of 965 person-visits and the altered equation (the "new CKiD equation") estimated GFR within 30% of the measured value 91% of the time. [12]

The equations described above have been developed for a population with subnormal GFR and their accuracy is not known for children with a normal or supranormal GFR, a category into which many children with cancer fall. In addition the purpose of monitoring GFR in our patient population is to determine the safety of delivering full-dose chemotherapy, the threshold for which is 60-70mL/min/1.73m² in most protocols.

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Blufpand et al evaluated a CysC based equation, the “Filler equation”, in children having treatment for malignancy. [13] This study included children with a range of GFRs including mild dysfunction. They demonstrated that this equation more accurately estimated GFR than a creatinine based equation. Laskin et al evaluated multiple CysC based equations in children receiving autologous stem cell transplantation and found that the best performing equation was the “new CKiD equation” described above. [14] They found that the equation had a 100% sensitivity for detecting GFR < 100mL/min/1.73m² and 80.8% accuracy within 30% of measured GFR.

We compared 4 equations which estimate GFR with the gold standard of isotopic measurement: the Schwartz formula using creatinine, the Filler equation using cystatin C, and the CKiD and newCKiD formulae using Cystatin C and creatinine. We sought to assess the accuracy of GFR estimation by CysC based equations in a cohort of children with solid and CNS tumours receiving nephrotoxic chemotherapy.

Methods

With institutional ethics approval, we performed a prospective assessment between October 2014 and October 2015 of children with solid and CNS tumours receiving nephrotoxic chemotherapy. With every isotopic GFR measurement, paired CysC and creatinine were measured and recorded. Allowance was made for up to a week between measurement of CysC/creatinine and isotopic GFR provided no chemotherapy was administered in between measurements.

CysC was determined using a particle-enhanced turbidometric immunoassay (COBAS 501) according to manufacturer instructions. Creatinine was calculated using an IDMS traceable enzymatic assay (Vitros® chemistry). Isotopic GFR measurements were all taken using a single injection of Tc-99m-DTPA at a fresh injection site with measurements in blood at 2 time points – 90 minutes and 180 minutes post injection. GFR was calculated using a slope intercept method. Estimated GFR was calculated using the CKiD, [9] new CKiD, [12] Filler, [15] and Schwartz creatinine-based equations (Supplementary table I). [4] For adolescent males (13-18 years), the constant used in the Schwartz equation was 0.7. [16] Statistical analysis was performed using the base package in the R language. [17] Bland-Altman analysis of difference was performed.

Cost analysis was performed using the billed cost per test for CysC and DTPA GFR measurement at our institution. Cost savings were calculated on average per child receiving nephrotoxic chemotherapy.

Results

Fifty seven paired CysC and isotopic GFR measurements were analysed. The majority of paired tests were performed on the same day with the longest period between blood tests and isotopic GFR being 5 days. No patient received chemotherapy in the intervening period between a set of measurements. One set of measurements was excluded as the child was receiving hyperhydration at the time of the CysC measurement, lowering the reading to well below normal range. No patient received steroid for at least 7 days before measurement of CysC and none had suspected or confirmed thyroid hormone abnormalities. Details of the patient cohort are shown in table I.

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The majority of isotopic GFR measurements were normal with 84% at or above 90mL/min/1.73m² and 70% at or above 100mL/min/1.73m². The best performing equation of the four analysed was newCKiD. For this equation 45% of calculated values were within 10% of measured values and 86% were within 30% of measured values. This outperformed the other equations in our cohort as seen in table II and accuracy is similar to the original description of this equation. [12]

Figure 1 shows the relationship between isotopic GFR and estimated GFR using the newCKiD equation. For GFR values measured at below 70mL/min/1.73m² the highest estimated value was 85mL/min/1.73m². All values estimated at over 100mL/min/1.73m² had measured values greater than 90mL/min/1.73m² which accounted for 66% of the data set. 15 sets of tests were taken from children aged under 3 years. Figure 2 plots the relationship between isotopic GFR and estimated GFR using the newCKiD equation for this age group. Again all values estimated at over 100mL/min/1.73m² had measured values greater than 90mL/min/1.73m². Bland-Altman analysis was performed and Figure 3 shows a Bland-Altman plot for the cohort. Bias for the newCKiD equation was small and not statistically significant at -4.6mL/min/1.73m² (95% C.I. -10 – 0.7). Most of the variance occurred at the higher ranges of GFR with all of the data points outside the limits of agreement appearing above a value of 150mL/min/1.73m² (see Figure 3).

DTPA GFR measurement is costed at AUD\$158.35 and CysC is costed at AUD\$22. We assumed an average of 3 measurements of renal function per child receiving nephrotoxic chemotherapy meaning a cost of AUD\$475.05 per child. Given the data shown, if isotopic GFR had been avoided for all children with an estimated GFR of >100mL/min/1.73m² the cost per child would have been, on average, AUD\$224.35, a cost reduction of more than 50%.

Discussion

CysC based equations have an established place in the estimation of GFR in children with chronic renal disease. [9-11] This report adds to a growing body of evidence that it could be used in place of isotopic GFR measurement for the majority of children with solid and brain tumours receiving nephrotoxic chemotherapy.

The information sought in the assessment of renal function of children receiving chemotherapy is fundamentally different to that being sought for children with chronic kidney disease. In the chemotherapy group information is sought about deteriorating GFR or GFR below the range at which chemotherapy is safely given at full dose. Small changes in the value of GFR are less important, whereas in the chronic kidney disease group this is a critical detail. In addition, the range of GFR in the chronic kidney disease group is generally subnormal whereas the majority of children receiving chemotherapy have normal GFR. [13] The validation of equations using CysC to estimate GFR have generally been conducted on cohorts of children with significantly subnormal GFR and this validation does not necessarily hold true for GFR in the normal range. [9,12]

Despite the increasing evidence that creatinine-based estimation of GFR is inaccurate this continues to be an accepted method of renal assessment in many chemotherapy protocols for children with cancer. [5] At our institution we have not relied on creatinine-based estimation of GFR for some time and have pursued isotopic GFR measurement at regular time-points for accurate renal

assessment. This practice is reflected in all other centres in Australasia (Personal communication Drs Gottardo, Kellie, Lyver, Hassall, Ziegler, Kirby, Laughton - 2 December 2015). Whilst this provides accurate information it requires at least 4 hours of time for the child and family in addition to the siting of an intravenous cannula which may be traumatic.

CysC based estimation has the advantage of eliminating the time and distress of an isotopic GFR and, as shown here, has enough accuracy to answer the question being asked in the majority of situations. We propose that if estimated GFR as determined by the newCKiD equation is greater than 100mL/min/1.73m^2 that the actual GFR is highly likely to be above 90mL/min/1.73m^2 and, as such, isotopic GFR is not necessary.

Although our cohort included children as young as 6 months, the accuracy of GFR estimation in young children has not been conclusively established. In our cohort 15 measurements were taken on children under the age of 3 and similar accuracy was achieved, insofar as all estimated GFR values above 100mL/min/1.73m^2 had measured GFR above 90mL/min/1.73m^2 . Given the paucity of information, caution is advised for patients under 3 years.

Given the growing evidence of their inaccuracy, removing creatinine-based equations from paediatric oncology practice may be warranted. This report is consistent with other reports in showing the accuracy of CysC-based equations in estimating GFR and the role they could play in replacing many instances of isotopic GFR measurement in our patients. We show that, in our cohort, on two thirds of occasions, isotopic GFR can safely be avoided in favour of a simple and inexpensive blood test. As shown above, there is a resultant cost saving with this approach also, although this is a secondary goal.

There are two instances which may be present in the paediatric oncology setting which affect the serum concentration of CysC. Corticosteroid therapy influences the level of CysC in a largely dose-dependent manner, [18] thus GFR estimated by CysC level in children taking corticosteroids is likely to underestimate the true GFR. Some children having treatment for solid and central nervous system tumours will require steroids either for antiemesis or for management of tumour-associated oedema. Thyroid dysfunction can affect CysC levels but the degree of impact is not clear so CysC must be interpreted with caution in patients with thyroid dysfunction. [19,20]

There are many published equations for using CysC to estimate GFR. The question of which equation to use is not simple but we believe that the newCKiD equation is the most appropriate. It was devised based on the largest published sample of paediatric patients and has been well validated on an independent set. The drawback is that the equation has not been conclusively validated at normal or supranormal GFR in children. This need not provide an obstacle to its use, given the sensitive detection of subnormal GFR is the goal in our population. We did show a greater variance at normal and supranormal GFR (Figure 3) but this does not impact on the ability of this equation to direct safe omission of isotopic GFR for patients in this range.

Some studies in adults have suggested that CysC based equations may not accurately reflect changes of GFR during or after treatment with nephrotoxic chemotherapy. [21, 22] Our contrasting findings

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may be explained by the fact that the equation used in our cohort takes into account variables other than just CysC. Alternatively, CysC may be a more reliable predictor of GFR in children than adults.

An issue which is not addressed by the current study is the ability of CysC based equations to track declining GFR over time within individual patients where the GFR remains above the values utilised for reducing chemotherapy. Given the increased variance at normal or supranormal GFR there remains doubt as to the ability of the equations tested to accurately achieve this and future studies would be required to assess this additional utility.

Another limitation to the implementation of this equation in practice is the mathematical difficulty in calculation. The potential for error in calculation is considerable given the number of different values raised to the power of decimals. Ideally equations such as this should be calculated within clinical biochemistry departments and the results reported directly to clinicians. Failing this, accuracy can be maximised by embedding the correct equation in spreadsheet software or a simple web or mobile application and making this available among a department or institution.

A final limitation is the different methods of measuring CysC. Particle-enhanced turbidometric immunoassay (PETIA) and particle-enhanced nephelometric immunoassay (PENIA) use slightly different techniques to measure the concentration of CysC in a sample. There are slight differences in the values produced but this is largely confined to values of CysC in excess of 2.5mg/L, corresponding to significantly subnormal GFR. [23] We do not believe that this impacts significantly on the population in question here or the question being asked of them. Interestingly, the newCKiD equation (based on a PENIA assay) performed better in our population than the original CKiD equation (based on a PETIA assay) despite CysC being measured by a PETIA assay in this cohort.

The use of the newCKiD equation can lead to the safe omission of isotopic GFR for around two thirds of instances of renal function assessment in paediatric oncology patients with solid or CNS tumours receiving nephrotoxic chemotherapy. [12] Where estimated GFR is above 100mL/min/1.73m² there is a high likelihood that the actual GFR is above 90mL/min/1.73m² and, provided this does not represent a significant drop in GFR from previous measurements, isotopic GFR can be safely avoided.

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Figure Captions

Figure 1. Correlation between calculated GFR based on the New CKiD formula and isotopic GFR – all patients. Horizontal line at 70mL/min/1.73m² below which chemotherapy doses are often altered. Vertical line at 100mL/min/1.73m² below which we recommend isotopic GFR measurement.

Figure 2. Correlation between calculated GFR based on the New CKiD formula and isotopic GFR – patients under 3. Horizontal line at 70mL/min/1.73m² below which chemotherapy doses are often altered. Vertical line at 100mL/min/1.73m² below which we recommend isotopic GFR measurement.

Figure 3. Bland-Altman plot investigating variance and bias. Dashed lines represent 95% confidence intervals around each labelled solid line.

Supplementary table I: Equations Used to Estimate GFR

Table I. Clinical Details

Age	Mean	8.2 years
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	Range	6m - 17 years	
		Number	%
Sex	Male	26	46
	Female	30	54
Diagnosis	Solid tumour	35	63
	CNS tumour	21	37

Table II. Accuracy of 4 Equations at Estimating GFR

Formula	Reference	Within 30% of measured GFR	Within 10% of measured GFR
NewCKiD	12	86%	45%
CKiD	9	70%	29%
Filler	15	61%	25%
Schwartz	4	5%	2%

GFR – Glomerular filtration rate.

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Author/s:

Dodgshun, AJ;Quinlan, C;Sullivan, MJ

Title:

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Date:

2016-09-01

Citation:

Dodgshun, A. J., Quinlan, C. & Sullivan, M. J. (2016). Cystatin C Based Equation Accurately Estimates Glomerular Filtration Rate in Children With Solid and Central Nervous System Tumours: Enough Evidence to Change Practice?. PEDIATRIC BLOOD & CANCER, 63 (9), pp.1535-1538. <https://doi.org/10.1002/pbc.26043>.

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