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How to estimate GFR in children

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Introduction

The reference method to determine glomerular filtration rate (GFR) in children is the inulin clearance. Similarly, Cr51-EDTA, iohexol and iothalamate can be used as exogenous GFR markers [1,2]. Exogenous markers are expensive and rather impractical. Creatinine is by far the most commonly used biochemical marker of renal function. The commonest principle for assaying creatinine is the Jaffe reaction [3]. Since Jaffe only observed a complexation between picric acid and creatinine in alkaline environment and never described an analytical method, variation amongst 'Jaffe method' recipes is broad [4]. The analytical bias of current creatinine methods (due to interference by pseudochromogens and calibration differences) is still disappointing: the compensated Jaffe method shows a small positive bias, whereas a major positive bias is observed for the dry chemistry and the uncompensated Jaffe methods [5]. Interlaboratory variation for creatinine is still unacceptably high; recent studies have reported median method group variation coefficients of 6.4% at a concentration of 80 μmol/L [6]. Such variation leads to an unacceptable variation in the estimation of kidney function in young children and infants. Equations to estimate GFR require knowledge of the calibration of the serum creatinine assay [7].

Restandardization of creatinine

Recently, a new commutable serum creatinine reference material (NIST SRM 967) has become available. This material is value assigned with the gas chromatography isotope dilution mass spectrometry (GC-IDMS) and liquid chromatography isotope dilution mass spectrometry (LC-IDMS) reference measurement procedures. Implementing traceability of serum creatinine assays to the new standard material will lead to major changes in the clinical decision-making criteria currently used for serum creatinine and creatinine clearance [7].

In the earliest manual and automated methods, serum creatinine was assayed by the Jaffe reaction after deproteinization or dialysis, eliminating the pseudo-chromogen effect of proteins. Modern analysers use undiluted serum and plasma, making them prone to the so-called protein error in the alkaline picrate reaction [8]. In the serum of adults, this effect produces a positive difference of ∼27 μmol/L (±0.3 mg/dL) creatinine compared with HPLC or enzymatic methods [8]. Because urine contains relatively little or no protein, the protein error affects only creatinine determinations in serum or plasma. Therefore, creatinine clearance is underestimated when creatinine methods affected by protein error are used. For calculating GFR, this systematic positive bias is greatly compensated by the overestimation attributable to tubular secretion of creatinine, which is relatively more important in children [8].

Serum or plasma creatinine values are often used for estimating GFR [8]. For adults, the currently recommended estimating equation has been developed from the Modification of Diet in Renal Disease (MDRD) Study [9]. The current variability in the calibration of serum creatinine assays introduces a source of error into GFR estimates. In particular, variability in creatinine calibration and measurement imprecision contributes to substantial uncertainty in estimating GFR in children, who usually have lower serum creatinine concentrations than adults. The recent availability of the international NIST SRM 967 standard means an important milestone in the improvement of GFR estimation in adults [10].

Consequences of creatinine restandardization

For adults, an improved GFR-estimating equation based on serum creatinine values traceable to IDMS reference measurement procedures has been presented [7]. Manufacturers can restandardize their Jaffe creatinine assays using a so-called compensation, a mathematical correction that compensates for analytical non-specificity due to the protein error. Since children show lower reference ranges for total protein, this protein error is considerably smaller [11]. In consequence, use of restandardized Jaffe-type assays results in overcompensation when used in children or infants (occasionally even leading to negative values in children with a decreased muscle mass!). Enzymatic methods manage to

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Table 1. Example of creatinine-based GFR estimation problems in a 4-year-old boy (height 100 cm)

Analytical method	Serum creatinine (mg/dL)	GFR-Schwartz (mL/min)	GFR-Counahan (mL/min)
Non-compensated Jaffe	0.71	77.5	60.6
Compensated Jaffe (adapted to SRM 967)	0.41	134.1	105
Enzymatic (adapted to SRM 967)	0.47	117	91

measure the serum creatinine more correctly. Due to the elimination of analytical non-specificity, the lower enzymatic creatinine result (when the result has not been adjusted to Jaffe-like results) leads to markedly increased creatinine clearance and GFR values because of the increased effect of tubular secretion. Paradoxically, the analytical improvement makes creatinine less suited as a GFR marker in paediatric medicine [11]. When creatinine clearance is measured in patients who have been administered cimetidine, the effect of tubular secretion can be corrected [12]. However, this method cannot be used on a wide scale.

The bias in serum creatinine concentration in the lower range is a major concern in paediatrics due to the much lower reference ranges for serum or plasma creatinine in infants and children [13,14]. For estimating GFR in children and infants, the Schwartz [15–17] and the Counahan–Barratt equations [18] are recommended. Both provide GFR estimates based on a constant multiplied by the child's height divided by the serum creatinine concentration. The values for the constant used in both equations differ considerably: $k = 38$ (Counahan) versus $k = 48.7$ (Schwartz) [19]. Since these formulas have been validated 30 years ago (using Jaffe recipes that are no longer on the market), reassessment of classical formulas for estimating creatinine clearance and GFR using modern assays is strongly recommended. Despite the major change in values caused by the recent standardization, so far no clinically validated adaptations of creatinine-based formulas for estimating GFR in children have been published. It is clear that this will be difficult; compensated Jaffe results will be less suited than enzymatic methods as a base for these calculations. Theoretically, the expression kL/(creatinine) (in which k is a constant and L the child's length) could be replaced by kL/[(creatinine; IDMS calibrated) + non-specificity correction] when using the new IDMS-calibrated assays. However, this non-specificity correction shows a variation [8] that increases the uncertainty of the estimation. It is clear that extreme care will have to be taken since coefficients will depend on the method chosen. Table 1 illustrates the GFR estimation problems in children due to creatinine standardization.

Alternative markers

Serum concentrations of low-molecular-weight marker proteins are primarily determined by GFR. Cystatin C (Cys C) is a 13 kDa cysteine protease that is produced by all nucleated cells [13,20]. The gene is of the house-keeping type, which is compatible with a stable production rate even in the presence of inflammatory stimuli. As a GFR marker in paediatric populations [21], serum Cys C levels generally show diagnostic superiority or equivalence of serum Cys C versus serum creatinine. Especially in the blind range of creatinine, Cys C proves to be a superior marker. Unlike creatinine, serum Cys C reflects renal function in children independent of age, gender, height and body composition [21]. Clinicians should be cognizant of a number of caveats (upregulation in certain tumours, glucocorticoid treatment, thyroid dysfunction) that can influence Cys C results [22,23]. Serum creatinine values are lower in malnourished children and lead to overestimation of GFR, while Cys C levels are unaffected [24].

In comparison with the Schwartz formula, Cys C-based GFR estimates show significantly less bias and serve as a better estimate for GFR in children [25]. International standardization for Cys C by an International Federation of Clinical Chemistry (IFCC) working group is nearing completion. Beta trace protein (BTP) is a 23–29 kDa protein, which has been introduced for the measurement of kidney function in the creatinine-blind range [7,26]. Beta 2-microglobulin has been advocated as a GFR marker [7], but its serum concentration can increase as an acute-phase reactant or as a tumour marker in lymphoproliferative disorders [7].

Next steps

Between-laboratory variation of Jaffe-based methods has not decreased over the last decade, despite technical progress [5]. Analytical bias in creatinine assays needs to be reduced and non-specificity bias should be improved and, if necessary, adapted to a paediatric serum matrix. The creatinine standardization issue has major clinical consequences that are far beyond the significance of the parameter itself. Apart from the conventional calculation of the creatinine clearance, also the calculation of the clearance using derived formulas is a key element in the assessment of renal function and the dose calculation of many drugs [27]. Many existing drug dosage schemes have been based using poorly described non-specific 'Jaffe' methods.

When introducing revised serum creatinine calibration traceable to IDMS, laboratories will need to communicate with paediatricians and pharmacists: serum creatinine reference intervals will drop, calculations of estimated GFR used by pharmacists or other health care professionals to adjust drug dosages will be affected by the decreased creatinine values, measured and calculated creatinine clearance values and GFR values will increase, and their corresponding reference intervals will be different.

In view of the difficulties in adapting creatinine assays to the new calibrators in the paediatric concentration range in a uniform way, the low-molecular-mass proteins Cys C and BTP offer promising alternatives for calculating GFR, in particular in children with a decreased muscle mass or in the blind range of creatinine. In comparison with serum creatinine, low-molecular-mass proteins have a better diagnostic sensitivity for detection of impaired GFR [13,21]. Although some caveats have to be taken into account when interpreting test results [22,23], the protein-based GFR

calculations only require serum values. The ongoing progress in the standardization of these protein assays will enable the wide-scale use of these methods.

Conflict of interest statement. None declared.

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