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ASSESSMENT OF RENAL FUNCTION FROM PLASMA UREA AND PLASMA CREATININE IN CHILDREN

J. Brøchner-Mortensen, B. Hammerich and J. Christoffersen

From the Departments of Clinical Physiology and Paediatrics, Aalborg Sygehus, Aalborg, Denmark

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Abstract. The diagnostic value of plasma urea and plasma creatinine, used separately and in combination, for assessment of renal function in children was determined from simultaneously measured values of plasma urea, plasma creatinine and glomerular filtration rate (GFR) in 357 children with different nephro-urological disorders. GFR was determined from the total [^{51}Cr]EDTA plasma clearance measured by a reliable single injection method. Four levels of renal function (with the limits expressed as % of the age-dependent normal mean standard GFR) were defined: normal (>75%); moderately decreased (75–52%); considerably decreased (51–28%); and severely decreased (<28%). Plasma concentrations of urea (mmol/l) and creatinine (expressed as a percentage of age-dependent normal mean value) were graded into low and high normal, moderately increased, considerably increased and severely increased values. Only by using plasma urea and plasma creatinine in combination all four levels of renal function could be predicted in the individual child with a high degree of certainty (probability 0.94–1.00). The results of the study indicate that the plasma concentration of urea and creatinine should be measured simultaneously, the results being used in combination with due consideration to the variability of plasma creatinine with age. By this procedure the majority of children, i.e. approximately 80%, with nephro-urological disorders who are referred to a paediatric clinic can have their level of renal function predicted with a high degree of certainty. Using plasma urea and plasma creatinine separately the corresponding figure is 50 and 60%, respectively.

It is generally accepted that the glomerular filtration rate (GFR) is the best single parameter for assessing renal function. Determination of GFR in children is most often used to assess whether—and to what extent—the combined function of the two kidneys is affected by an actual nephro-urological disorder, and to assess changes of the renal function in the course of disease.

In daily clinical work, determination of the plasma urea concentration is more widely used than plasma creatinine determinations as a first choice to assess renal function in children. In contrast to plasma creatinine, the level of plasma urea is not dependent on age, in children (Schwartz, Haycock & Spitzer, 1976) so that, from a practical point of view, the evaluation of a plasma urea value versus normal reference values is more easy to handle than that for plasma creatinine.

In children suffering from various nephro-urological disorders we have in the present study evaluated the reliability of plasma urea, plasma creatinine (with due consideration to its variation with age) and combinations hereof to predict the level of renal function. The aim of this new approach in children was to test when and to what extent the plasma parameters in question can replace a further assessment via determination of GFR by a reliable clearance method.

MATERIAL AND METHODS

Patients

The present material constitutes children aged 1–14 years. GFR and the concentrations of urea and creatinine in plasma were determined simultaneously in a non-fasting state in the morning. No standardization with respect to hydration or preceding protein intake was aimed at. At the time of examination none of the children had oedema. The patients were divided into two groups.

Group 1 consisted of 216 *selected* examinations in 198 children (median age 7.9 years, range 1.1–14.9 years) who from January 1976 to May 1978 were referred to the Department of Clinical Physiology for renal function examinations. In those children with normal renal function who had more than one examination, only the results from the first were used. Due to the low incidence of impaired renal function, the results from all determinations (=45) in 27 children with decreased renal function were used. Distribution of the 198 children according to diagnosis was glomerular nephropathies (31), renal and urinary tract malformations (111), urinary tract infection without malformations (44) and other nephro-urological disorders (12).

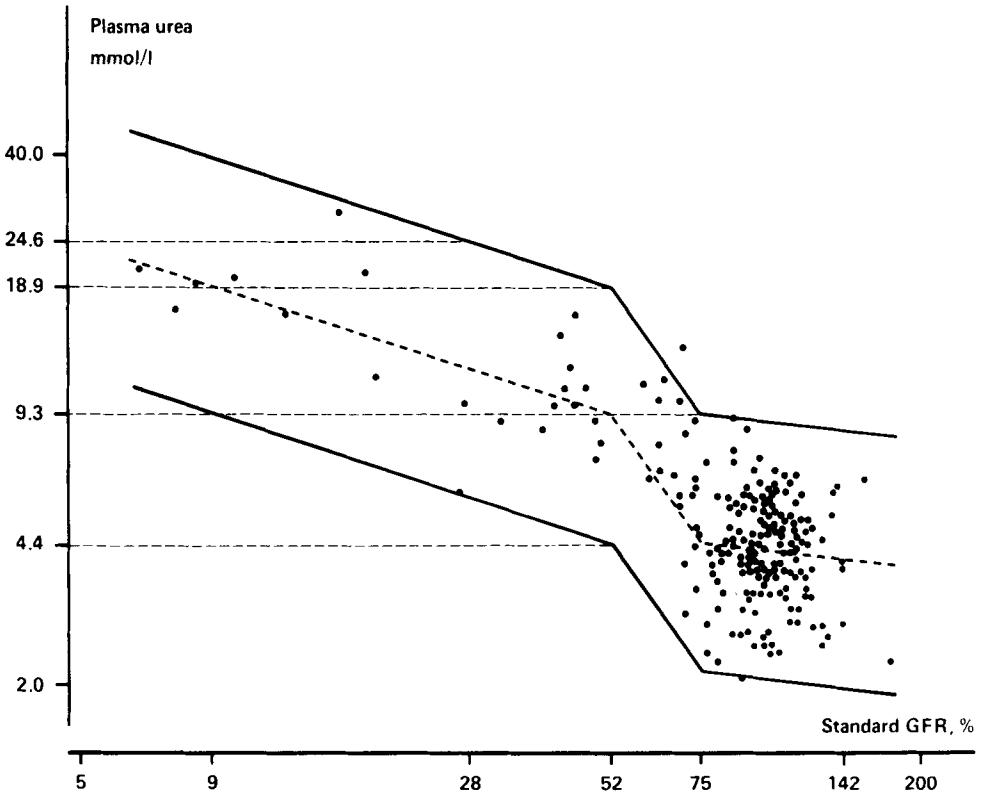

Fig. 1. Comparison of plasma urea concentration (mmol/l) and standard glomerular filtration rate, GFR, (expressed as % of normal mean), in 198 children (216 cases). The non-horizontal interrupted lines indicate the regression lines, and the solid lines indicate the 99% confidence limits: ±0.3148 (log value). The horizontal hatched lines indicate (from below) the upper limits of low normal, high normal, moderately increased, and considerably increased plasma urea concentrations.

Group 2 consisted of a *consecutive* series of 159 children (median age 8.0 years, range 1.6–14.5 years) referred from June 1978 to October 1979 from the Department of Paediatrics for renal function examinations. The children suffered from the same nephro-urological disorders as the children in group 1. Relative distribution according to normal and different degrees of decreased renal function was 0.818 (normal), 0.094 (moderately decreased), 0.075 (considerably decreased) and 0.013 (severely decreased).

Table I. *Delimitation of normal and varying degrees of decreased renal function*

The limits are given as percentages of the age-dependent normal mean standard GFR

Normal	Moderately decreased	Considerably decreased	Severely decreased
>75%	75–52%	51–28%	<28%

Methods

GFR was determined from the total [^{51}Cr]EDTA plasma clearance measured by a simplified single injection method (Brøchner-Mortensen, Haahr & Christoffersen, 1974; Brøchner-Mortensen, Rohbrandt & Lauritzen, 1977). The concentration of urea and creatinine in plasma was determined on a Technicon SMA® 12/60 autoanalyser.

Standard GFR, i.e. GFR corrected to a body surface area of 1.73 m^2, increases with age to achieve a stable level at the age of 2 years (Chantler, 1973). Standard GFR in the individual patient was therefore expressed as a percentage of the corresponding age-dependent normal mean value. The mean value of standard GFR (using the present clearance method) is 109 ml/min (coefficient of variation = 12%) in healthy children more than 2 years of age (Brøchner-Mortensen, Ditzel & Rødbro, 1979). From this mean value and the published data by Winberg (1959) on the endogenous creatinine clearance as a function of age in children, we calculated standard GFR on age in children aged ≤2.0 years to be

$$\log \text{standard GFR} = 0.209 \log \text{age (days)} + 1.44. \quad (1)$$

Table II. *Delimitations of plasma urea and plasma creatinine for assessment of renal function*

Plasma urea (mmol/l)					Plasma creatinine (% of age-dependent normal mean)				
Low normal	High normal	Moderately increased	Considerably increased	Severely increased	Low normal	High normal	Moderately increased	Considerably increased	Severely increased
≤4.4	4.5–9.3	9.4–18.9	19.0–24.6	>24.6	≤118	119–184	185–293	294–483	>483

As stated in Table I, ranges for normal renal function and three different degrees of decreased renal function were defined by successive subtraction of twice the coefficient of variation (=24%) from normal mean (=100%).

The individual plasma creatinine concentration was expressed as a percentage of the corresponding age-dependent normal mean value:

$$\text{Plasma creatinine } (\mu\text{mol/l}) = 1.94 \text{ age (years)} + 34.0 \quad (2)$$

Equation [2] corresponds to the regression of plasma creatinine concentration on age in normal children of both sexes (Schwartz, Haycock & Spitzer, 1976) multiplied with the factor 1.045. This factor was used to correct for the difference between creatinine concentration values determined by the method used by Schwartz et al. (1976) and ours.

CALCULATIONS

The correlation between plasma creatinine and renal function in children with glomerulopathies in group 1 did not differ from that in children with other nephro-urological disorders. The same holds true for plasma urea. The results from all children in group 1 could thus be used to determine the nosographic probabilities of plasma urea and plasma creatinine for assessment of renal function using different levels of the two plasma parameters and combinations hereof.

Delimitations of plasma urea, plasma creatinine and combinations thereof

Plasma urea. After logarithmic transformation of the values for plasma urea and renal function the best correlation between these was determined by calculating the regression of plasma urea on considerably and severely decreased renal function, and on normal renal function, respectively. Thereafter, the regression line corresponding to the values of moderately decreased renal function was constructed by drawing a line between the end points of the two afore-mentioned regression lines. The regression lines, together with the 99% confidence limits (=±2.5×0.1259), are shown in Fig. 1.

The four horizontal hatched lines in Fig. 1 indicate from below: the upper limit of low normal plasma urea (keeping all patients with considerably decreased renal function above this line); the upper limit of high normal plasma urea (keeping all patients with normal renal function below this line); the upper limit of moderately increased plasma urea (keeping all patients with moderately decreased renal function below this line); and the upper limit of considerably increased plasma urea (keeping all patients with considerably decreased renal function below this line). The limits of the five different levels of plasma urea concentrations are summarized in Table II.

Plasma creatinine. The best correlation between the values of plasma creatinine and renal function was determined by regression analysis in the same way as that for plasma urea. The regression lines together with the 99% confidence limits (=2.5×0.0789) are shown in Fig. 2. The horizontal hatched lines were drawn in analogy with the lines in Fig. 1, and the limits of the five different levels of the normalized plasma creatinine concentrations are given in Table II.

Combined use of plasma urea and plasma creatinine. The employed seven different combinations are defined in Table III.

Nosographic and diagnostic probabilities of plasma urea, plasma creatinine and combinations thereof

The lower limit of severely decreased renal function was set to 9%; the upper limit of normal renal function to 142% (cf. Figs. 1 and 2). The nosographic probability for each of the four levels of renal function with respect to each of the five levels of plasma urea and plasma creatinine was determined from the regression analysis shown in Figs. 1 and 2 together with tables of the standardized normal distribution (Documenta Geigy, pp. 28–30). From the thus determined probabilities the corresponding probabilities with respect to each of the seven combination of plasma urea and plasma creatinine were determined using the multiplication theorem. Using Bayes's theorem (Wulf, 1976) the diagnostic probabilities were determined from the nosographic probabilities in group 1 (Tables IV and V) combined with the relative distribution in group 2 according to the four levels of renal function. From the same data, the expected distribution in group 2 according to the five levels of plasma urea–creatinine and combinations thereof was calculated.

RESULTS

Nosographic probabilities of plasma urea, plasma creatinine and combinations hereof

The figures are given in Tables IV and V. The salient data in these two tables concern the probabilities for children with different degrees of de-

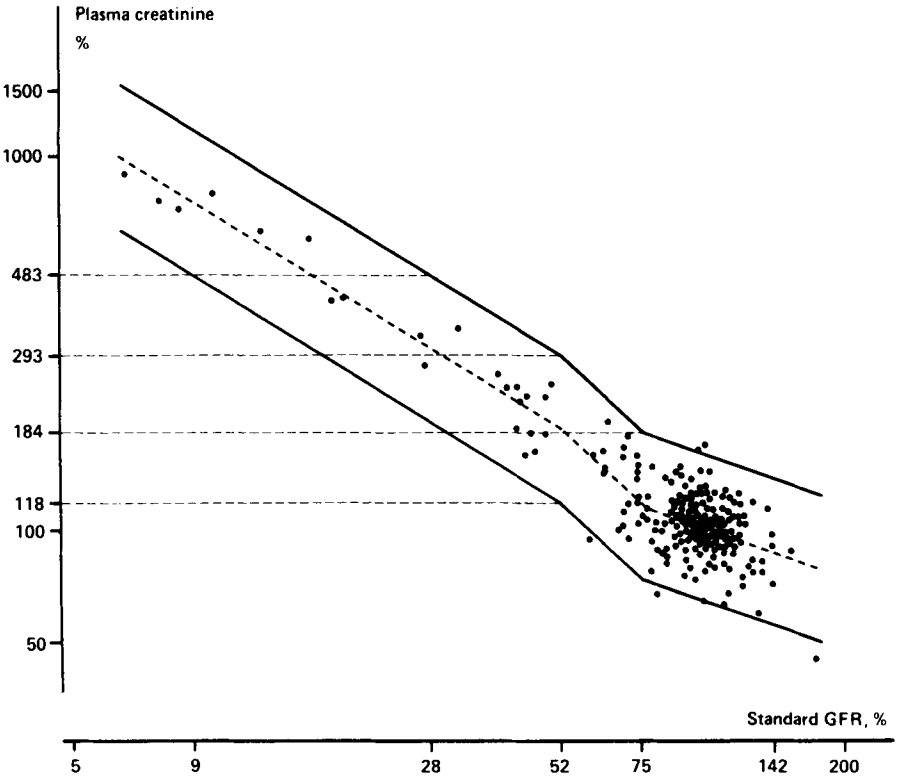

Fig. 2. Comparison of plasma creatinine concentration (expressed as % of age-dependent normal mean value) and standard glomerular filtration rate, GFR, (expressed as % of normal mean), in 198 children (216 cases). The non-horizontal interrupted lines indicate the regression lines, and the solid lines indicate the 99% confidence limits: ±0.1973 (log value). The horizontal hatched lines indicate (from below) the upper limits of low normal, high normal, moderately increased, and considerably increased plasma creatinine concentrations.

Table III. *Combined use of plasma creatinine and plasma urea at different levels for assessment of renal function*

Combination	Plasma urea		Plasma creatinine
1	Low normal	or	Low normal
	Low normal	or	High normal
	High normal		Low normal
2	High normal		High normal
3	Low normal	or	Moderately increased
	Moderately increased		Low normal
4	High normal	or	Moderately increased
	Moderately increased	or	High normal
	Moderately increased		Moderately increased
5	High normal	or	Considerably increased
	Considerably increased		High normal
6	Moderately increased	or	Considerably increased
	Considerably increased	or	Moderately increased
	Considerably increased		Considerably increased
7	Severely increased	and/or	Severely increased

Table IV. *Nosographic probabilities of plasma urea and plasma creatinine for assessment of renal function*
Within each group of renal function the first and second row indicates the probabilities for plasma urea and plasma creatinine, respectively

Level of plasma urea and plasma creatinine	Renal function							
	Normal		Moderately decreased		Considerably decreased		Severely decreased	
Low normal	0.554	0.728	0.244	0.266	0.000	0.000	0.000	0.000
High normal	0.446	0.272	0.512	0.467	0.349	0.206	0.094	0.000
Moderately increased	0.000	0.000	0.244	0.267	0.626	0.495	0.630	0.091
Considerably increased	0.000	0.000	0.000	0.000	0.025	0.299	0.182	0.409
Severely increased	0.000	0.000	0.000	0.000	0.000	0.000	0.094	0.500

creased renal function to have a concentration of urea and/or creatinine in plasma within normal range (low normal–high normal). Using plasma urea and plasma creatinine separately, these parameters were within normal range in about 75% of the children with a moderately decreased renal function. The corresponding figure for the combined use of plasma urea and plasma creatinine (combinations 1 and 2) was 55%, but only 32% using combination 1. None of the children with a severely decreased renal function had plasma creatinine concentrations within normal range. On the other hand this was the case for plasma urea in 9%.

Diagnostic probabilities of plasma urea, plasma creatinine and combinations hereof

Plasma urea and plasma creatinine (Table VI). The probability for a correct prediction of the corresponding level of renal function (figures in italics) was about the same for plasma urea and plasma creatinine, with the exception of considerably increased values where plasma creatinine was superior to plasma urea. The probability for a correct prediction of a normal and a severely decreased renal function was very high (0.95–1.00) using low normal and severely increased values, respectively. A thus correct prediction is to be expected in approximately 48 and 63% of the children, using plasma urea and plasma creatinine, respectively.

Combined use of plasma urea and plasma creatinine (Table VII). There was a good correspondence between the expected and found relative distribution according to the seven combinations. The diagnostic value of combination 1, 3, 5 and 7 to predict a normal, moderately, considerably and severely decreased renal function, respectively, was very high with probabilities in the range of 0.94–1.00. A thus correct prediction is to be expected in approximately 78% of the children, 75% being children with combination 1.

DISCUSSION

The purpose of the present study was to evaluate the diagnostic value of plasma urea, plasma creatinine, and combinations hereof to assess renal function in children with different nephro-urological disorders. To do this it is essential that GFR is determined with a reliable method. The single injection method used gives an accurate measure of GFR in children without peripheral oedema and the precision of the method is very high (Brøchner-Mortensen et al., 1974; Brøchner-Mortensen, Rohbrandt & Lauritzen, 1977). At the time of examination none of the children had oedema (which tends to overestimate GFR) and only in a few children it was necessary to defer the examination until

Table V. *Nosographic probabilities of combined use of plasma urea and plasma creatinine for assessment of renal function*
Definition of the combinations is given in Table III

Combination	Renal function			
	Normal	Moderately decreased	Considerably decreased	Severely decreased
1	0.879	0.315	0.000	0.000
2	0.121	0.239	0.072	0.000
3	0.000	0.130	0.000	0.000
4	0.000	0.316	0.612	0.066
5	0.000	0.000	0.109	0.038
6	0.000	0.000	0.207	0.349
7	0.000	0.000	0.000	0.547

Table VI. *Diagnostic probabilities of plasma urea and plasma creatinine for assessment of renal function*

The figures in parentheses indicate the expected relative number of the different levels of plasma urea and plasma creatinine in the studied population (group 2). Correspondence values between plasma urea–creatinine and renal function are given in italics

	Level of plasma urea and plasma creatinine									
	Low normal		High normal		Moderately increased		Considerably increased		Severely increased	
Renal function	Pl. urea (47.6%)	Pl. creat (62.1%)	Pl. urea (44.1%)	Pl. creat (28.2%)	Pl. urea (7.8%)	Pl. creat (6.3%)	Pl. urea (0.4%)	Pl. creat (2.7%)	Pl. urea (0.1%)	Pl. creat (0.7%)
Normal	*0.952*	*0.960*	*0.829*	*0.789*	0.000	0.000	0.000	0.000	0.000	0.000
Moderately decreased	0.048	0.040	0.109	0.156	*0.294*	*0.396*	0.000	0.000	0.000	0.000
Considerably decreased	0.000	0.000	0.059	0.055	0.601	0.585	*0.442*	*0.808*	0.000	0.000
Severely decreased	0.000	0.000	0.003	0.000	0.105	0.019	0.558	0.192	*1.000*	*1.000*

the presence of periphereal oedema had disappeared.

In patients with glomerulopathies, particularly in those with nephrotic syndrome, the ratio between the endogenous creatinine clearance and GFR tends to be higher than that in patients with other nephro-urological disorders (Brøchner-Mortensen, 1978; Ikkos & Strøm, 1955; Mattar, Barnett, McNamara & Lauson, 1952). Accordingly, for the same GFR value the plasma creatinine concentration should on average be lowest in the former group of patients. None of the present children had clinical signs of nephrotic syndrome at the time of examination which probably explains why we could not demonstrate the afore-mentioned expected difference between the 31 children with glomerulopathies and the 167 children with other nephro-urological disorders (group 1). This finding allowed a grading of plasma creatinine concentrations irrespective of the nature of renal disease. The same holds true for plasma urea concentrations.

The close correspondence between the expected and found relative distribution according to the seven combinations of plasma urea and plasma creatinine at different levels in group 2 (cf. Table VII) furthermore indicates that the calculated nosographic probabilities in group 1 can be considered representative for children with nephro-urological disorders (children with nephrotic syndrome not included).

On the other hand, our results on the diagnostic value of plasma urea, plasma creatinine and combinations hereof are not applicable on populations who differ essentially from our group 2 with respect to relative distribution of the four levels of renal function. This probably holds true for children referred to special units of paediatric nephrology.

Table VII. *Diagnostic probabilities of combined use of plasma urea and plasma creatinine for assessment of renal function*

Within each combination the first and second figure in parentheses indicate the expected and found relative number of children, respectively, in the population studied (group 2). Key to the combinations is given in Table III

	Combination						
Renal function	1 (74.9%, 73.0%)	2 (12.7%, 15.1%)	3 (1.2%, 0.0%)	4 (7.6%, 9.4%)	5 (0.9%, 0.0%)	6 (2.0%, 2.5%)	7 (0.7%, 0.0%)
Normal	0.960	0.780	0.000	0.000	0.000	0.000	0.000
Moderately decreased	0.040	0.177	1.000	0.389	0.000	0.000	0.000
Considerably decreased	0.000	0.043	0.000	0.600	0.943	0.774	0.000
Severely decreased	0.000	0.000	0.000	0.011	0.057	0.226	1.000

However, knowing the prevalence of the four levels of renal function, the diagnostic value of plasma urea, plasma creatinine and combinations hereof can be calculated for *any* population of children from the here reported nosographic probabilities.

The nosographic approach to evaluate the usefulness of plasma urea and plasma creatinine clearly demonstrated the superiority of using plasma urea and plasma creatinine in combination. Approximately 75% of the children with moderately decreased renal function had a plasma concentration of urea and creatinine within normal range, i.e. 75% of children with a moderately decreased renal function (75–52% of normal mean) are overlooked when plasma urea and plasma creatinine are used separately for assessing renal function. Corresponding results have been reported in adult patients (Brøchner-Mortensen, Jensen & Rødbro, 1977; Rickers, Brøchner-Mortensen & Rødbro, 1978). On the other hand, combined use of plasma concentrations of urea and creatinine within normal range (combination 1) minimised the number of missed cases with a moderately decreased renal function from 75 to 32%, and none of the children with a more impaired renal function (considerably and severely decreased) were considered to have a normal renal function.

The results here presented on diagnostic probabilities concern the reliability of the different tests (plasma urea, plasma creatinine and combinations thereof) to predict the level of renal function in the individual child. The prediction of a normal renal function in a child either having a low normal plasma urea, a low normal plasma creatinine or combination 1 was equally very reliable (probability 0.95–0.96), but a child with combination 1 is much more frequently met with than a child with a low normal plasma urea or a low normal plasma creatinine among children with nephro-urological disorders referred to a paediatric clinic. The same holds true for combination 7 versus a severely increased plasma urea (both predicting a severely decreased renal function correctly), and only by using plasma urea and plasma creatinine in combination (combinations 3 and 5) a child's renal function can be predicted to be moderately or considerably decreased, respectively, with a high degree of certainty.

Based on the present results on nosographic or diagnostic probabilities we recommend that the plasma concentration of urea and creatinine is measured simultaneously, the results being used in combination with due consideration to the variability of plasma creatinine with age. To make this procedure suitable for daily clinical work the laboratory should for instance classify the results to one of the seven combinations so that prediction of the individual child's level of renal function can be read by the clinician from Table VII.

In children belonging to the same population as the present group 2 (i.e. children with nephro-urological disorders referred to a paediatric clinic) approximately 80% will turn out to have combination 1, 3, 5 and 7 from which the renal function level can be predicted with a high degree of certainty (cf. Table VII). In these children no further assessment is needed with the exception of those cases where the clinician finds it essential—from a therapeutic or prognostic point of view—to determine a child's renal function with the highest degree of reliability. In these cases we determine GFR from the total [^{51}Cr]EDTA plasma clearance measured by a very reliable simplified single injection method either using venous or capillary blood sampling (Brøchner-Mortensen & Christoffersen, 1977; Brøchner-Mortensen et al., 1974; Brøchner-Mortensen, Rohbrandt & Lauritzen, 1977). GFR is also determined by the single injection method in children with combination 2, 4 and 6 since these combinations only give a rough prediction of the renal function level (cf. Table VII).

To assess changes of the renal function in the individual child, as a function of time, GFR is generally only determined by the single injection [^{51}Cr]EDTA clearance method if the combined use of plasma urea and plasma creatinine is changed from one combination to another, or if the normalized plasma creatinine concentration shows a steady increase or decline. Justification of this procedure is at present under investigation.

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