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Research Article

# Urinary Creatinine from Multiple, Random Samples for Estimating Diuresis in Children

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## Abstract

**Background:** Quantifying urinary output may be important for the management of few clinical conditions associated with either polyuria (diabetics insipidus, acute or chronic renal tubular disorders) or with poor fluid intake (kidney stones). Self-reported fluid intake or 24-hours urinary collection (UC) may be unreliable for objective evaluation given the several sources of error and the variability of fluid intake and needs related to changes in temperature and physical execise. In order to simplify and objectify the measurement of urine output (uO), we hypotesized that urinary creatinine concentration from multiple spot urine samples (US) of different days can accurately estimate individual diuresis. **Methods**: The present cohort study enrolled 14 healthy subjects (F=7), aged 3.9-12.6 years, who were all coauthors' offspring. Seventy UC (5 per subject), for measuring uO, and the related 400 US (1 per voiding), to determine urinary creatinine concentration (uCr), were collected. The mean of 5 measured uO (MuO) served as individual reference value. The UC were used to generate (by regression analysis) the equation predicting mean MuO from mean uCr (of 5US) (=41.76-0.12 x mean uCr). The performance of Calculated uO (CuO) from over 50,000 possible means of 5 US randomly taken in different days was analysed as to precision and accuracy (P25 and P30). **Results**: The mean MuO and CuO were 30.6 and 32.0 mL/kg/day, respectively. The mean difference between the individual reference value and a single MuO or the CuO were 6.4 and 3.8 mL/kg/day (equivalent to 20.1 and 12.4% of the reference value). The maximal difference between the reference value and the MuO or the CuO were 13.6 and 8.9 mL/kg/day (equivalent to 44.4 and 29.2% of the reference value). The accuracy of MuO *vs* CuO, measured as P25 and P30, were respectively 65.7 *vs* 80.1% and 80.0 *vs* 85.4%.**Conclusion**: In the described optimal experimental conditions (for all subjects being children of pediatricians and coauthors), uO was estimated more accurately (and practically), by the mean uCr of 5 random urine samples taken in different days than with UC. In real life, with several types of error systematically affecting UC and not urine sampling, the superiority of CuO is likely to be even greater.

**Keywords:** Urinary creatinine concentration; Children; Urine Samples

**List of abbreviations:** **Cr:** creatinine; CuO: calculated urinary output; MuO: measured urinary output; **P25:** the percentage of estimates within 25% of the gold standard; **P30:** the percentage of estimates within 30% of the gold standard; **u:** urinary; **UC:** urinary collection; **uO:** urinary output; **US:** urinary samples; **yo:** years old

## Introduction

In few clinical conditions characterized by polyuria (diabetes insipidus, polydipsa, interstitial nephritis, acute or chronic renal tubular disorders) [1,2] or related to poor fluid intake (kidney stones) [3], it may be of some importance to estimate urinary output (uO). However, particularly in children, the direct measurement of uO requires 24-hours urine collection (UC) that may be quite unpractical and can be inaccurate because of several types of error (miscounting of time and volume, missed voidings, enuresis, incomplete bladder voiding, etc.). Furthermore, UC is often performed during weekends, thus it may poorly represent the usual fluid intake. Finally, the UC may represent a significant obstacle to perform population studies focused on fluid intake and/or uO.

We hypotesized that the mean uCreatinine (uCr) from multiple spot urine samples, randomly collected in different days, can generate an accurate estimate of uO in children given that spot urine sampling is not affected by any of the mentioned sources of error and can be easily repeated and performed during weekdays.

## Materials and Methods

The study was designed to perform a head-to-head comparison of accuracy between uO as determined with UC and with uCr from multiple random urine samples collected in different days. A unique methodological feature of the present study is that all the enrolled subjects were children of pediatricians and coauthors of the study itself, in order to assure maximal adherence to the protocol when performing the UC and when collecting urine samples.

### Study subjects and sampling protocol

Healthy children of both gender, all offspring of hospital pediatrician and coauthors of the present study, were enrolled and studied in 5 non-consecutive days. For each of the 5 days, participants (and the related caregivers) were instructed to collect all the urine produced during the 24 hours and 1 urine sample (3 mLs) for each voiding. The samples taken were counted in the total urine volume of the UC. In case a single voiding was missed the UC was repeated.

### Measurements

Urinary Cr was determined, by standard methods, in each of the voiding samples. The mean of the 5 UC was identified as the individual reference value. An equation to predict mean uO from uCr, defined as calculated uO (CuO), was derived by means of the regression analysis (see below). Measured uO (MuO) were compared to CuO from all the possible means of 5 random samples taken in different days (with the only condition of no more than 1 sample per day). The mean and maximal deviation between the reference value (mean uO) and both the MuO and the CuO, were also determined and compared.

### Development of the equation

For each of the enrolled subjects and for each of the 5 studied days, a regression analysis was performed between the reference value (x variable) and the mean uCr (y variable). Out of all the separate regression lines, a "common" linear models was derived and the corresponding equations was used to predict the reference value, in mEq/Kg/day, through the mean of uCr obtained from all the possible combinations of all the available random urinary samples.

### Analysis

The study considered 2 criteria for performance of the CuO: accuracy and bias.

Accuracy was measured by P25 and P30 (the percentage of estimates respectively within 25 and 30% of the gold standard) and a P30 >85% qualified the method as satisfactory for clinical purposes. Bias was defined as the mean difference between the reference value and the CuO.

Data are presented in absolute numbers and percentage, mean with standard deviation and median with interquartile range depending on the distribution of the variables. Statistical analysis was performed using Student's t test for paired data.

## Results

Participants were 14 healthy children (7 females) and all of them were offspring of the coauthors. All together, the subjects performed 70 24hUC (5 per subject) to measure uO and collected a total of 400 urine samples (one per voiding) to determine CuO. Table 1 shows the general characteristics of participants whose median age (and IQR) was 6.9 years (5.5-7.9), the median weight was 20.7 kg (16.4-23.5) and the mean uO (+SD) was 30.6+6.1 mL/kg/day without significant gender differences (31.2+6.6 in females and 29.9+6.1 in males; p: 0.709). The mean CuO was 32.0+2.8 mL/kg/day, again without significant gender differences: males 32.5+2.3 and females 31.6+3.3 mL/kg/day; p: 0.493. Figure 1 shows the inverse correlation between MuO and uCr that

represents the premesis for deriving the formula to predict uO from uCr with a Person's correlation coefficient of 0.774 ($p<0.0001$). Figure 2 (Panel A) compares the mean and maximal difference between the individual uO (reference value) and MuO vs CuO. Both values were significantly lower with CuO, in particular the mean difference and the maximal difference (as percentage of the reference value) were 20.1 vs 12.4% and 44.4 vs 29.2%. The same figure 1 (Panel B) shows that also the accuracy (measured as P25 and P30) of MuO vs CuO was lower: 65.7 vs 80.1% and 80.0 vs 85.4%.

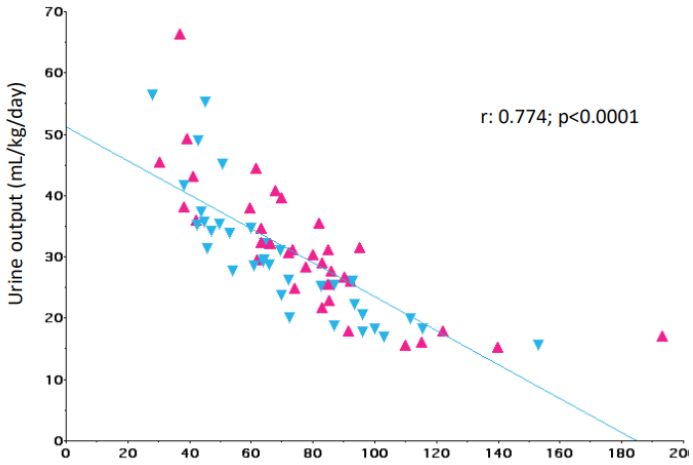


**Figure 1:** Correlation between daily urinary output and urinary creatinine of 24hr collection in males (blu) and females (pink).

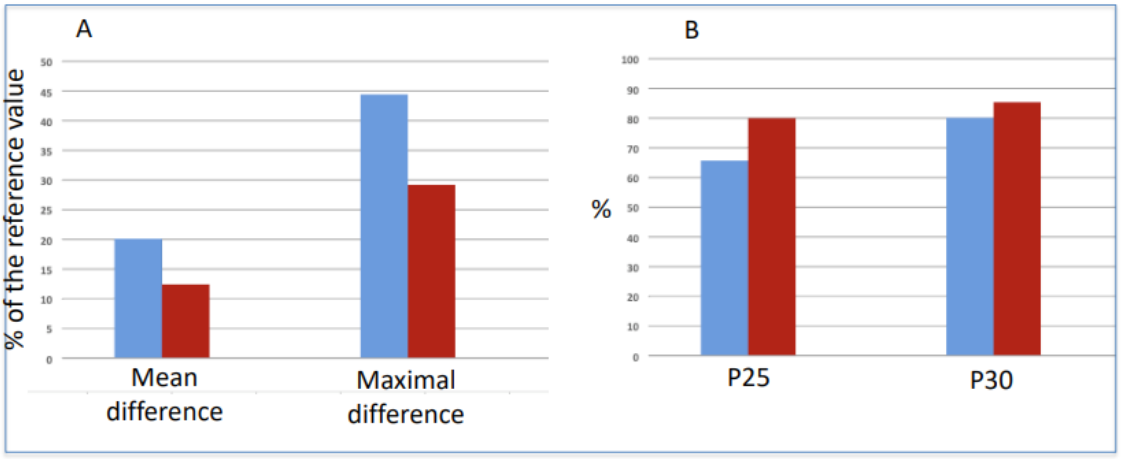


**Figure 2:** Panel A compares the mean and maximal difference, as percentage of the reference value (gold standard), of urinary output as measured with a single 24-hours urine collection (in blue) and calculated (in red) from all the possible means of uCreatinine derived from multiple (n: 5) urine samples randomly taken in different days and collected simultaneously with urine collections. Panel B provides the respective accuracy figures as measured by P25 and P30.

| 24hUC | | | | | | | | | | Multiple sampling from voidings of 24hUC | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subject | Gender | Age (yrs) | Weight (kg) | No of 24h UC | Measured uQ[1] mL/kg/ Gold Standard | Deviation of single 24hUC to Gold Standard mL/kg/d (%) | | P25 P30[2] % (of single 24hrUC) | | No. of samples | No. of possible combination of 4 samples in different days | Calculated uQ[3] mL/ kg/d | Deviation to measured uQ (Gold standard-calculated) mL/kg/d (%) | | P25 P30[2] % (of all possible means) | |
| | | | | | | Mean | Max | | | | | | Mean | Max | | |
| #1 | F | 11 | 38.9 | 5 | 36.7 | 7.6 (20.7) | 12.5 (34.1) | 80 | 80 | 31 | 5,999 | 34.2 | 3.0 (8.2) | 8.0 (21.8) | 100 | 100 |
| #2 | M | 3.9 | 15.2 | 5 | 38.3 | 10.0 (26.1) | 18.3 (47.8) | 60 | 60 | 28 | 5,040 | 34.1 | 3.9 (10.2) | 7.5 (19.6) | 100 | 100 |
| #3 | M | 5.6 | 21.2 | 5 | 35.3 | 8.8 (24.9) | 20.0 (52.2) | 60 | 60 | 34 | 5,995 | 34.9 | 1.2 (3.4) | 7.2 (20.4) | 100 | 100 |
| #4 | F | 5.5 | 16.1 | 5 | 36.0 | 4.6 (12.8) | 9.4 (26.1) | 80 | 100 | 25 | 3,000 | 35.6 | 1.5 (4.2) | 6.1 (16.9) | 100 | 100 |
| #5 | F | 7.6 | 23.5 | 5 | 27.1 | 5.1 (18.9) | 15.6 (57.6) | 60 | 80 | 23 | 2,800 | 30.9 | 3.6 (13.3) | 7.9 (29.2) | 98 | 100 |
| #6 | M | 6.3 | 19.9 | 5 | 30.7 | 2.4 ( 7.8) | 4.5 (14.7) | 100 | 100 | 31 | 5,995 | 33.5 | 3.1 (10.1) | 6.9 (22.5) | 100 | 100 |
| #7 | M | 7 | 19.8 | 5 | 25.1 | 3.0 (12.0) | 5.9 (23.5) | 80 | 100 | 24 | 3,000 | 31.4 | 6.3 (25.1) | 11.7 (46.6) | 48 | 75 |
| #8 | M | 7.2 | 20.5 | 5 | 32.9 | 8.1 (24.6) | 16.0 (48.6) | 60 | 60 | 26 | 5,184 | 33.2 | 1.5 (4.6) | 9.0 (27.6) | 100 | 100 |
| #9 | M | 5.5 | 16.4 | 5 | 21.0 | 3.7 (17.6) | 5.4 (25.7) | 80 | 100 | 18 | 540 | 27.9 | 6.9 (32.9) | 11.1 (52.9) | 16 | 19 |
| #10 | F | 7.9 | 21 | 5 | 35.5 | 7.3 (20.6) | 17.9 (50.4) | 60 | 80 | 25 | 1,800 | 30.2 | 5.3 (14.9) | 12 (33.8) | 95 | 99 |
| #11 | F | 6.7 | 22.5 | 5 | 18.4 | 2.7 (14.7) | 7.1 (38.6) | 80 | 80 | 40 | 5,995 | 25.2 | 7.1 (38.6) | 13.4 (72.8) | 10 | 17 |
| #12 | F | 12.6 | 42.4 | 5 | 30.9 | 3.7 (12.0) | 9.2 (29.8) | 80 | 100 | 38 | 3,840 | 32.3 | 1.4 (4.5) | 5.2 (16.8) | 99 | 100 |
| #13 | F | 10.3 | 36.5 | 5 | 33.9 | 13.0 (38.3) | 32.4 (95.6) | 40 | 60 | 28 | 4,800 | 31.8 | 2.1 (6.2) | 7.5 (22.1) | 100 | 100 |
| #14 | M | 5.2 | 15.6 | 5 | 26.1 | 9.4 (35.9) | 15.6 (59.8) | 0 | 60 | 29 | 5,400 | 32.8 | 6.7 (25,7) | 11.7 (44.8) | 63 | 85 |
| **Means** | **-** | **7.3** | **23.5** | **5** | **30.6** | **6.4 (20.1)** | **13.6 (44.4)** | **65.7** | **80.0** | **28.6** | **4,242** | **32.0** | **3.8 (12.4)** | **8.92 (29.2)** | **80.1** | **85.4** |

**Table 1:** Legend: M; Male; F: Female; yrs: years; kg: Kilogram; d: Day; 24hUC: 24 hour urine collection; Max: Maximal difference; 1. Mean of the 5 24hUCs; 2. Percentage of estimates respectively within 25 and 30% of the gold standard; 3. Mean of all the possible combinations of 5 samples randomly taken in 5 different days.

## Discussion

The present study shows that uO, as calculated from the mean uCr of 5 urine samples randomly taken in different days, is more accurate than that measured by UC.

In the clinical practice, the measurement of uO might not be particularly important except for few conditions characterized by, associated with or consequent to excessive or inadequate uO and/or fluid intake. However, when the estimation of uO is necessary, a reliable quantification, by means of UC, may be troublesome not only for the physician but also for patients and/or parents. In fact, even when performed with attention, UC can be affected by several types of error. Patients may miscount the urine volume, because they are just not equipped for precise measurement, particularly when the volume is small, as in young children, or very large as in conditions associated with polyuria. In other cases (or in addition) the time elapsed from the beginning to the end of the UC, is miscounted. Among the most common errors done by patients when performing UC is the wrongful keeping of the first voiding, with (or without) discarding the last voiding. Furthermore, some voidings might be missed either voluntarily or unconsciously. In addition, particularly in children, a UC can be impossible for age-related incontinence or can be very difficult for enuresis, despite patient's positive attitude and efforts. Finally, the sampling of a partial volume of the UC may also be a pre-analytic source of error out of the physician's control, particularly in polyuric patients. UO derived from multiple samples by means of a formula, has the advantage that spot samples are not burdened by any of the described sources of error.

Urinary Cr concentration in spot samples will obviously and greatly vary during the day, however the measurements performed on different days minimize the risk of combining samples under- or overestimating the mean value. This concept is clearly supported and demonstrated by the maximal deviation for the most outlier combinations of multiple samples in the order of 8.9 mL/kg/day equivalent to 29% of the reference value (much lower than the maximal deviation observed by measuring uO with UC which is in the range of 13.6 mL/kg/day equivalent to 44% of the reference value).

Moreover, UC are often performed during weekends when the patient can stay at home and more conveniently follows the instructions received by physicians for collecting them. This approach will systematically bias the estimation of uO for the different type of food and fluids consumed at home compared to school days. On the contrary, urine sampling is feasible any day with a consequent more accurate representation of the usual uO.

Our study, focused on children, includes a methodological approach that, in our opinion, provides high reliability to the results: all tests were performed under special vigilance being the enrolled subjects all children of physicians, coauthors of the study itself. The comprehension of the procedure and the commitment to the importance of being extremely precise in collecting the many urine samples and in measuring both the time and the volume of UC, provide an extra and unique guarantee that the study measurements were accurate and may represent an important strength of the investigation.

A major limitations of the present study is the relatively reduced number of enrolled subjects, nevertheless our findings and the conclusions are based on a total of 70 UC and more than 50 thousand possible combinations of uCr from multiple urine samples.

An additional limitation is that the presented formula was derived from caucasian healthy children and its applicability to patients and/or to other age and/or to other ethnic groups need to be demonstrated as it is for subjects with specific diseases.

We think that the availability of an easy and reliable method to estimate uO and, by that, the intake of fluids, may greatly enhance investigations on the potential role of fluid intake in some clinical conditions towards the identification of new preventive or therapeutic strategies as was done in a previous paper of ours [4].

## Conclusions

In the described unique and optimal experimental conditions (for the specific commitment to the study purpose of involved subjects) uO was estimated more precisely, accurately and practically, by the mean of 5 uCr taken in 5 different days rather than with a single UC. In real life, with various sources of error systematically affecting UC, but not samplings, we speculate that measured uO might have an even lower precision and accuracy. Calculated uO from 5 random urine samples should be preferred over 24hUC, in a similar way to how other urinary parameters on spot urine samples are now preferred over determinations on 24hUC [5,6].

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### Article summary

In children diuresis can be accurately estimated by urinary creatinine from multiple, random spot samples rather then with urinary collection

### What's known on the subject

The standard of care for estimating diuresis is based on 24 hour urinary collection. However this method is time consuming, unpractical and often imprecise.

### What this study adds

We provide evidence that urinary output can be precisely and accurately estimated with urinary creatinine on 5 urine samples taken in different days

### Contributors' statement

Gianluigi Ardissino, Laura Martelli, Patrizia Salice, Valeria Daccò, Maria Cristina Villa, Martino Masciani, Alice Monzani, Maria Cristina Mancuso performed the urinary collections and the multiple urine sampling.

Antonio Vergori and Cesare Vergori performed data analysis, developed the equation used to calculate diuresis from urinary creatinine and provided the informatic support for calculating the several thousands of means of the 5 samples from different days

Patrizia Salice, Valentina Capone, Maria Cristina Mancuso, Annalisa Bosco, Mariaelena Albion, Stefania Rotondo participated in the study design, in processing the samples and the analysis of results.

All co-authors participated in the writing of the paper or in its improvement. They all read and approved the final version as submitted and agree to be accountable for all aspects of the work.

**Conflict of interest:** The authors have no conflict of interest relevant to this article to disclose

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