Age Related Nocturnal Urine Volume and Maximum Voided Volume in Healthy Children: Reappraisal of International Children's Continence Society Definitions

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Purpose: We determined normal, age related reference data regarding maximum voided volume and nocturnal urine production using the same methodology as in clinical practice.

Materials and Methods: A total of 62 girls and 86 boys without enuresis (mean ± SD age 9.64 ± 2.63 years, range 3 to 15) completed 4 days (2 weekends) of frequency-volume charts and 14 days of home recording of nocturnal urine production. From these recordings maximum voided volume with and without first morning void was derived for each subject. Also, average nocturnal urine volume with and without nocturia was calculated. Percentiles were produced by dividing the population into 1-year age groups.

Results: Based on 2,836 daytime voids and 1,977 overnight recordings, maximum voided volume and nocturnal urine volume showed a significant linear relationship with age but not with gender. Maximum voided volume with first morning void was significantly higher than without (403 ± 137 ml vs 281 ± 112 ml, p <0.0001) and the 50th percentile line of maximum voided volume with first morning void was 80 to 100 ml higher than Koff's formula (30 × [age + 1] ml). Conversely the 50th percentile of maximum voided volume without first morning void was almost identical to Koff's formula. Regarding nocturnal measurements, nocturia was noted on 128 nights (6.5%) and nocturnal urine volume on nights with nocturia was significantly higher than on nights without nocturia (365 ± 160 ml vs 248 ± 75 ml, respectively, p <0.0001). The 97.5th nocturnal urine volume percentile line of healthy children deviated markedly from the current International Children's Continence Society definition of nocturnal polyuria, especially at low and high ages.

Conclusions: We demonstrate clearly that the universally used formula 30 × (age + 1) ml is indeed valid for a population of healthy Danish children but only if the first morning void is disregarded. Furthermore, we question the validity of the current International Children's Continence Society formula for nocturnal polyuria (nocturnal urine volume greater than 130% of maximum voided volume for age), and instead we propose the formula, nocturnal urine volume greater than 20 × (age + 9) ml.

Key Words: nocturia, polyuria, urinary bladder, urination disorders

Abbreviations and Acronyms

AVV = average voided volume

FV = frequency-volume

ICCS = International Children's Continence Society

MVV = maximum voided volume

MVV_{age} = expected maximum voided volume for age

MVV_{w} = maximum voided volume with morning voided volume included

MVV_{wo} = maximum voided volume without morning voided volume included

N-Uvol = nocturnal urine volume

N-$Uvol_{w}$ = nocturnal urine volume with nocturia nights included

N-$Uvol_{wo}$ = nocturnal urine volume without nocturia nights included

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Study protocol was approved by Danish Data Protection Agency and regional committee on biomedical research ethics.

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ALTHOUGH no data exist regarding the exact prevalence, there is substantial evidence that increased nocturnal urine output and decreased nocturnal bladder capacity together with some form of arousal impairment are pre-

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dominating pathogenic factors in monosymptomatic nocturnal enuresis. Of these conditions nocturnal urine output and bladder capacity are hypothesized to be clinically useful variables when characterizing underlying mechanisms and predicting response to different treatment modalities.[1–3] Supporting this hypothesis, use of desmopressin to reduce nocturnal urine production and use of enuresis alarm to increase maximum voided volume are the preferred modalities to treat monosymptomatic nocturnal enuresis worldwide, either as monotherapy or in combination.[4–6]

There is currently no direct method available in practice to determine nocturnal bladder capacity in patients with monosymptomatic nocturnal enuresis. Instead, various estimates of daytime bladder capacity have been suggested, eg free voided volume, cystometric capacity and cystographic capacity. The most commonly used surrogate estimate of bladder capacity is MVV observed on FV chart or some hours after a fluid load.[7,8] Especially the former was observed to predict effectively response to desmopressin,[2] whereas the latter failed to do so in a comparative study.[3] Recording of MVV from the FV chart bears methodological controversies and it is still unclear whether the first morning void should be included. Furthermore, accurate age related reference values using the same recording methodology as in daily practice are lacking.

Abnormally high nocturnal urine volume has been substantiated on wet nights, at least in a subpopulation of patients with monosymptomatic nocturnal enuresis.[9–11] The initial findings were based on inpatient circadian studies, and confirmed by home recording of the difference in diaper weight before and after sleep.[12] The current ICCS definition of nocturnal polyuria (nocturnal urine volume on a wet night greater than 130% expected MVV for age) is based mainly on expert opinion and not on normal age related reference data.[13] Therefore, we determined age related reference data obtained from healthy children without enuresis regarding MVV and nocturnal urine production using the same methodology as in current clinical practice.

MATERIALS AND METHODS

The study protocol was approved by the Danish Data Protection Agency and the regional committee on biomedical research ethics, and informed consent was obtained from all participants. A total of 155 healthy children were recruited through hospital staff members. Inclusion criteria were age 3 to 15 years, height and weight within 2 standard deviations of normal, no history of day or night urinary or fecal incontinence after age 4 years, no known current illness or use of any medications, drugs, alcohol or tobacco and normal urine dipstick analysis at study entry.

Study Design

During 2 weekends (total 4 days) children were asked to record the time and volume (by estimation) of all fluid intake and all voids (volumes were measured by a beaker with 20 ml markings). Also, during 14 days the children were asked to record their nocturnal urine volumes by emptying the bladder immediately before bedtime, and measuring the volume of any nocturia episodes and first morning void by a measuring beaker. No restrictions were applied on activity, meals, sleeping rhythm or drinking habits.

Statistical Methods

From the FV charts we calculated voiding frequency and average voided volume for each study day, and maximum voided volume with and without first morning void. A normal maximum voided volume for age was defined as 30 × (age in years + 1) ml.[14] Values are presented as mean ± SD unless otherwise stated. The 2.5th, 25th, 50th, 75th and 97.5th percentiles for the plot of MVV and N-Uvol vs age were calculated for intervals of 1 year from age 3 to 15 years, with the exception that all values less than 3 years were compiled as were values greater than 14 years. Regression lines were produced for each percentile (fig. 1). Comparison between boys and girls was analyzed by Student's t test. Correlations were sought by Pearson correlation analysis. For the statistical analysis we used SPSS®, version 17.0. A p value of less than 0.05 was considered statistically significant.

RESULTS

Study Subjects

We initially included 155 healthy volunteers, of whom 7 withdrew at an early stage and did not complete home recording. A total of 148 children completed the study and were included in the analysis (table 1). The 7 excluded subjects did not differ demographically from the group that completed the study. Analogous to the incontinence population there were more boys than girls (girl-to-boy ratio 0.72:1), which by chi-square test was not statistically significant. Boys were an average of 0.2 years older than girls ($p = 0.02$) but no other significant gender differences were observed.

Daytime Voided Volumes

A total of 140 children completed at least 3 days of sufficient quality recordings (2,836 total voided volumes). Seven children provided 2 days of recordings and 1 patient recorded only 1 day. Mean ± SD number of voids daily was 4.9 ± 1.1, with no significant difference between the 4 recording days (table 2). AVVs were also comparable on all 4 study days. MVV_{wo} (281 ± 112 ml) was markedly lower than MVV_w (403 ± 137 ml, $p < 0.0001$). MVV_{wo} ($r = 0.53$, $p < 0.001$) and MVV_w ($r = 0.60$, $p < 0.001$) exhibited a linear relationship with age. Furthermore, all age related percentiles revealed significant linear correlation with age regardless of inclusion or exclusion of first morning void

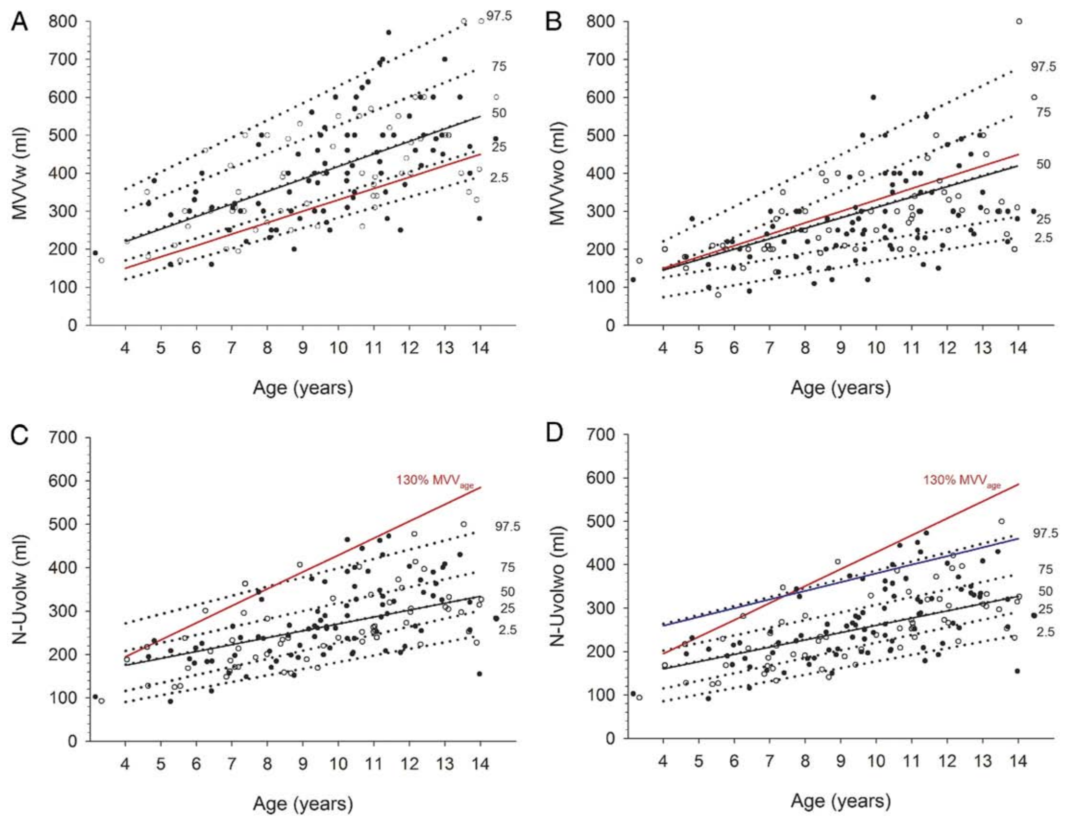

Figure 1. In 148 healthy children 3 to 15 years old maximum voided volumes were calculated from 4-day FV charts. *A*, results with first morning void included. *B*, results excluding first morning void. Red lines indicate MVV_{age} based on formula, 30 × (age + 1) ml. Dotted lines indicate 2.5th, 25th, 75th and 97.5th percentiles, and solid line indicates 50th percentile of study population. MVV_{age} is good estimate of 50th percentile of MVV_{wo} but markedly underestimates MVV_w. In same subjects average nocturnal urine volumes from 14 days of recording were calculated. *C*, results with nocturia. (*D*), results without nocturia. Red lines indicate current ICCS formula for nocturnal polyuria (130% of MVV_{age}). Dotted lines indicate 2.5th, 25th, 75th and 97.5th percentiles, and solid line indicates 50th percentile of study population. N-$Uvol_{wo}$ was lower than N-$Uvol_w$ spanning entire age range. Also, current ICCS definition was not parallel to 97.5th percentile of N-$Uvol_{wo}$. Blue line represents population based formula based on 97.5th percentile, 20 × (age + 9) ml.

(table 3). When comparing MVV_{age} with the 50th percentiles of MMV_w and MVV_{wo} it was evident that although the slopes of the relationships were comparable, MVV_w spanning the entire age range was approximately 80 to 100 ml higher than MVV_{age}, whereas MVV_{wo} approximated MVV_{age} to a much

Table 1. *Demographic data on 148 healthy children*

	Girls	Boys	Overall
No. pts	62	86	148
Mean ± SD age (yrs)*	9.51 ± 2.91	9.73 ± 2.42	9.64 ± 2.63
Mean ± SD birth wt (kg)	35.9 ± 12.8	31.7 ± 11.5	33.5 ± 12.2
Mean ± SD height (cm)	141.5 ± 18.3	136.7 ± 16.6	138.9 ± 17.5
Mean ± SD daytime voiding:			
Voids/day†	5.0 ± 1.0	4.7 ± 1.2	4.9 ± 1.1
Max morning voided vol (ml)	385 ± 128	352 ± 110	396 ± 134
MVV_{wo} (ml)	286 ± 118	277 ± 109	281 ± 112
MVV_w (ml)	394 ± 141	410 ± 134	403 ± 137
Nighttime voiding:			
No. nights with nocturia (%)	53 (6.3)	75 (6.6)	128 (6.5)
Mean ± SD AVV (ml)	188 ± 121	217 ± 109	204 ± 114
Mean ± SD N-$Uvol_{wo}$ (ml)	240 ± 79	254 ± 72	248 ± 75
Mean ± SD N-$Uvol_w$ (ml)	322 ± 152	390 ± 161	362 ± 160

* $p = 0.02$.
† $p < 0.05$.

Table 2. *Daytime voiding data during 4 days of recording in 148 healthy children*

	No. Pts	Mean ± SD AVV (ml)	Mean ± SD Voids/Day
Day 1	140	153 ± 97	5.2 ± 1.6
Day 2	138	153 ± 99	4.6 ± 1.7
Day 3	130	146 ± 94	4.8 ± 2.0
Day 4	139	149 ± 96	5.0 ± 1.5

higher degree. The statistical linear regression relationship between the 50th percentile MVV_{wo} and age was 28 × age + 36 ml, and similarly the 2.5th percentile MVV_{wo} was 16 × age + 10 ml.

Nocturnal Urine Volume

Home recordings of nocturnal urine volume were completed by all 148 children. We obtained 1,977 overnight recordings of an expected 2,072 (95.4%). Of the children 12 completed only 11 nights of recording and 47 did not complete the last night of recording. When analyzing the variation in average $N\text{-}Uvol_{wo}$ through time we found no significant difference among the 14 nights of recording (fig. 2). Average N-Uvol also showed considerable intraindividual variation, with an average coefficient of variation of 0.31 ± 0.07. Coefficient of variation was stable through the age range of the study. $N\text{-}Uvol_{w}$ and $N\text{-}Uvol_{wo}$ correlated significantly with age (r = 0.60, $p < 0.001$ and r = 0.61, $p < 0.0001$, respectively).

In 128 of the 1,977 recorded nights (6.5%) nocturia episodes were recorded. A total of 60 subjects (41% of the population) experienced 1 to 8 nights with nocturia during the 14 nights of recording. No subject recorded more than 1 episode of nocturia during the same night. In subjects who experienced nocturia the average nocturnal urine volume (365 ± 160 ml) was markedly higher during nights with nocturia than nights without nocturia (248 ± 75 ml, $p < 0.0001$). Average nocturia volumes correlated rather weakly with MVV_{wo} (r = 0.38, p = 0.003) and comprised an average ± SD of 85.7% ± 47% of the individual MVV_{wo}.

Figure 1 illustrates the 14-night average $N\text{-}Uvol_{w}$ and $N\text{-}Uvol_{wo}$ for each subject. Both estimates of nocturnal urine volume exhibited a linear relationship with age. Only 6 of the 148 subjects (4%) met the accepted ICCS definition of nocturnal polyuria regardless of nocturia status. However, the slope of the ICCS definition line was markedly different from both N-Uvol 50th percentile lines, and especially at the high age range there were considerable differences between the 2 variables. The statistical linear regression relationship between the 97.5th percentile $N\text{-}Uvol_{wo}$ and age was 20 × age + 180 ml. Finally we found a highly significant and positive correlation between $N\text{-}Uvol_{wo}$ and MVV_{wo} (r = 0.58, $p < 0.0001$).

DISCUSSION

Home recording of daytime maximum voided volume and nighttime urine production is an important diagnostic tool in the evaluation of children with urinary incontinence.[13] This is the first study to our knowledge to provide normal age related reference values for children using the same methods used in clinical practice. We demonstrate clearly that the universally used formula for age expected MVV_{age}, 30 × (age + 1) ml, is indeed valid for a population of healthy Danish children but only if the first morning void is disregarded. Furthermore, we question the validity of the current ICCS formula for nocturnal polyuria (N-Uvol greater than 130% MVV_{age}), as this relationship is far from the 97.5th percentiles of healthy children, especially in older children. Instead, the formula 20 × (age + 9) ml seems to be a valid estimate of the 97.5th population percentile.

Home recorded MVV on a free running cycle without any restrictions regarding fluid intake or physical activity is undoubtedly an inaccurate estimate of bladder capacity. However, despite inherent inaccuracy, MVV has proved to be an effective tool to predict response to desmopressin in children with nocturnal enuresis and response to standard uro-

Table 3. *Maximal voided volumes and nocturnal urine production by age*

Age (yrs)	No. Pts	Mean ml MVV_{wo} (range)	Mean ml MVV_{w} (range)	Mean ml $N\text{-}Uvol_{wo}$ (range)	Mean ml $N\text{-}Uvol_{w}$ (range)
Younger than 4	7	180 (120–280)	220 (170–380)	168 (93–231)	188 (93–231)
5	9	200 (80–220)	290 (160–350)	169 (91–229)	180 (92–238)
6	10	200 (90–240)	300 (160–460)	174 (116–281)	184 (116–301)
7	17	250 (140–350)	310 (195–500)	225 (132–347)	236 (149–363)
8	15	220 (110–400)	300 (200–530)	203 (141–406)	207 (152–407)
9	18	260 (120–600)	400 (250–600)	254 (169–374)	261 (169–374)
10	20	290 (200–500)	440 (260–640)	286 (201–444)	301 (201–465)
11	20	320 (150–550)	435 (250–770)	287 (178–472)	304 (205–473)
12	16	307 (170–500)	495 (400–600)	334 (223–421)	353 (223–478)
13	13	300 (200–500)	470 (280–800)	309 (155–499)	309 (155–500)
Older than 14	3	600 (200–800)	600 (490–800)	283 (282–326)	284 (282–326)

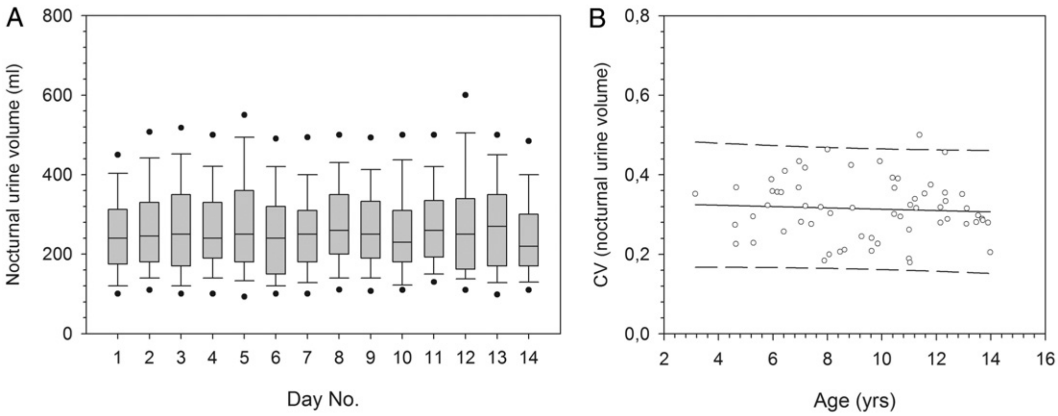

Figure 2. *A*, box plot of nocturnal urine volume in 148 healthy children during 14 nights of recording. Large interindividual variation was seen, but no systematic change, during 14 nights. *B*, individual coefficient of variation of nocturnal urine volume measurements during 14 nights plotted against subject age. Median coefficient of variation was approximately 30% and showed no relationship with age.

therapy in daytime incontinence.[3,15–18] Despite the widespread use of MVV measurements, no general consensus exists regarding either age related reference data used or method of measurement. By far the most widely used formula is 30 × (age + 1) ml, which in fact is an approximation of the originally proposed formula (age + 2 ounces), which correctly corresponds to 28.3 × (age + 2) ml.[14,19] This formula was not derived from FV charts, but was based on cystometric data in 35 anesthetized children.

Several studies contain bladder capacity data based on cystography in various patient populations with values above Koff's formula.[20–22] From these cystographic data it appears that the relationship between bladder capacity and age is linear only from age 2 to 4 years. Data derived from voided volumes have approximated Koff's formula when based on voids at a strong desire to void.[8,11] Other studies have used less than 4 days of recording and do not compare their results directly with Koff's data.[23,24] We reported previously in children with nocturnal enuresis that 2 weekends of FV charts were necessary to obtain a reproducible estimate of MVV_w.[12] Only 1 study based on single daily voids spanning 5 days compared voided volumes directly with Koff's formula and found lower values in 131 Japanese children.[25] However, based on 72-hour FV charts in 54 healthy children MVV_w values comparable to cystographic data from Kaefer et al[20] were reported by Van Hoeck et al.[23] A smaller patient population and a shorter recording period might at least partly explain the finding of lower MVV_w values compared to our study.

The present study was performed in 148 healthy Danish children and MVV data were derived from 2,836 voided volumes. Like others, we observed that more than 70% of the MVV_w estimates were found among the first morning voids and that no gender differences could be identified. From the MVV data we could produce age related population based percentiles (fig. 1). Ideally age related data, based on pediatric growth charts, should include longitudinal data where individual development through time can be incorporated. A limitation of the present study is that it is based entirely on cross-sectional data. Nevertheless, with this limitation in mind our data not only are useful to establish normal reference values for the 50th population percentile, but also allow evaluation of the degree of deviation from normal in each patient. Most studies on the role of reduced bladder capacity have used a cutoff value of less than 70% of Koff's formula.[2] However, from a statistical viewpoint the 2.5th percentile (16 × age + 10 ml) would be a more appropriate cutoff value for abnormality, and future studies should evaluate the clinical relevance of this definition.

Our results clearly reveal that MVV with first morning void was much higher than without first morning void (table 1 and fig. 1). Thus, MVV_w overestimated Koff's formula by approximately 80 to 100 ml, whereas the 50th percentile of MVV_{wo} was much closer to MVV_{age}. In fact the deviation between MVV_{wo} and MVV_{age} is less than 10 ml until age 8 years and lower than 25 ml until age 14 years. Therefore, as this difference is well within the inaccuracy of the estimate, we propose that Koff's formula continue to be used as the gold standard estimate of the 50th percentile of MVV for age with the caveat that morning voided volumes should be disregarded. Furthermore, using MVV_{wo} instead of MVV_w could be a theoretical advantage when evaluating bladder capacity in children with nocturnal enuresis, since these patients often cannot produce large morning voids due to the enuresis episodes.[23,26] In many studies of nocturnal enuresis it is not specified whether morning voids are included, although with our results in mind the prevalence of decreased MVV can change dramatically depending on the definition used.

In the present study we also noted a high day-to-day variation in nocturnal urine production with an average coefficient of variation of approximately 30%, albeit with no tendency toward a systematic change during the recorded days (fig. 2). One factor contributing to this variability is the occurrence of nocturia, as the urine volume on such nights was much higher than on nights without nocturia (table 1). This observation may correspond to cases of nocturnal enuresis, where N-Uvol is significantly higher during nights with enuresis.[27] As nights with nocturia in healthy children seem to resemble nights with polyuria in children with enuresis, we propose that nights with nocturia be disregarded when establishing normal nocturnal urine production data.

The current ICCS definition of nocturnal polyuria in enuresis (greater than 130% of MVV_{age}) is a pragmatic description not based on normal reference data but has been used by some to classify patient populations.[28–30] As shown in figure 1, our study demonstrates that although only approximately 5% of the N-Uvol data fall above the line of the ICCS definition, this relationship has a much higher slope than the 97.5th population percentile. Coincidentally the 2 estimates are almost identical around age 7 to 8 years, when many children with enuresis are evaluated, but deviate significantly at lower and higher ages. The formula for the 97.5th percentile N-Uvol, 20 $\times$ (age + 9 ml), has a similar slope compared to MVV_{wo} and seems to be a more appropriate estimate of nocturnal polyuria than the current ICCS formula. However, its value as a prognostic marker needs to be validated in larger studies.

CONCLUSIONS

We present population based, age related reference values for maximum voided volumes and nocturnal urine production in 148 healthy Danish children using the same methodology as in clinical practice. The 50th percentile line of MVV_{wo} (where morning voids are disregarded) falls close to the universally used formula, 30 $\times$ age + 30 ml, and we propose that this formula continue to be used as the gold standard. The 97.5th percentile line of nocturnal urine volume excluding nocturia is similar to the current ICCS formula only around age 7 to 8 years but deviates significantly at lower and higher ages. Therefore, we propose the 97.5th percentile, 20 $\times$ (age + 9 ml), to be validated as a future definition of nocturnal polyuria.

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EDITORIAL COMMENT

In the pathophysiology of nocturnal enuresis small nocturnal bladder capacity (maximum volume voided from a 48-hour frequency volume chart) and nocturnal polyuria are the usual suspects. In this study Rittig et al aim to provide reference values for both. They produce percentiles for MVV for age with and without first morning void. Their conclusion that MVV_{wo} is preferable to MVV_w to assess bladder capacity, since the median of MVV_{wo} follows Koff's formula more closely, can be challenged for 2 reasons. MVV_w is often the first void in the morning and larger than MVV_{wo}, supporting the hypothesis that nocturnal bladder reservoir function differs from the daytime and is better described by MVV_w (references 23 and 24 in article). Also, Koff's formula describes a population average, while the lower limit is of interest for studies of low bladder capacity. The 3rd percentile for cystographic bladder capacity is available from more than 2,000 observations (reference 22 in article), differing substantially from the MVV_{wo} 3rd percentile presented.

The authors also challenge the current ICCS definition of nocturnal polyuria with a new proposal, again including urine volume produced after a bedwetting event as a determinant. In prepubertal children without enuresis urine output decreases within 2 hours after bedtime to an average of 0.8 ml/kg per hour with a 95th percentile of 1.5 ml/kg per hour. Average urine production exceeds this rate before only 15% of bedwetting events.[1] Including nocturnal urine production following these events, as the current ICCS definition prescribes, identified only half of these events as polyuria.

Whatever definition of nocturnal polyuria or bladder capacity is proposed, randomized controlled trials revealing the potential to predict response to therapy remain a prerequisite for clinical application. For MVV the only randomized controlled trials to date have proved disappointing.[2]

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