The relationship between urinary calcium, sodium, and potassium excretion in full-term healthy newborns

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SUMMARY: Özkaya O, Buyan N, Erol İ, Atalay Y, Beyazova U, Şahin F, Söylemezoğlu O. The relationship between urinary calcium, sodium, and potassium excretion in full-term healthy newborns. Turk J Pediatr 2005; 47: 39-45.

The objective of this study was to determine the specific reference values for urinary calcium/creatinine (UCA/Cr) (mg/mg) in healthy breast-fed newborns, and to evaluate the relationship between UCa/Cr, urinary sodium/creatinine (UNa/Cr), urinary potassium/creatinine (UK/Cr) and UNa/UK ratios in the same group.

A total of 88 infants aged between 0-28 days were enrolled in this study. They were divided into two age groups as follows: Group I: ≤7 days of age; Group 2 infants aged between 8-28 days. Non-fasting spot urine was analyzed for Ca, Na, K and Cr.

Significant differences were observed between the two groups in terms of UCa/Cr (0.11 ± 0.10 vs 0.27 ± 0.23, $p < 0.001$), UNa/Cr (1.29 ± 1.63 vs 5.5 ± 4.83, $p < 0.001$), and UK/Cr (0.94 ± 0.99 vs 2.82 ± 2.3, $p < 0.001$). The data showed positive correlation between UCa/Cr and age ($r = 0.38$, $p < 0.001$) as well as between age and UNa/Cr ratio ($r = 0.68$, $p = 0.0001$) and between age and UK/Cr ratio ($r = 0.57$, $p < 0.0001$). Additionally, there was a positive correlation between UNa/UK and age ($r = 0.40$, $p = 0.001$). The UCa/Cr ratio positively correlated with UNa/Cr whereas no correlation was found between UCa/Cr and UNa/Uk ratio.

Our data suggest that the healthy neonates differ from the hypercalciuric patients by exhibiting a linear correlation between Na/K and UCa/Cr. As the normal values of UCa/Cr, UNa/Cr, UK/Cr, UNa/UK ratios in the early neonatal period differ from those in the late neonatal period, these differences should be taken into consideration when assessing urinary excretion of these parameters for diagnostic purposes in the early and late newborn periods.

Key words: newborn, urine, calcium, sodium, potassium.

Urinary calcium-creatinine (UCa/Cr) ratio in spot urine samples has been used extensively for both the screening and diagnosis of hypercalciuria (HC) since obtaining spot urine samples is easy and economic, and is a proxy for the results obtained from 24-h urine samples[1,2]. A UCa/Cr ratio >0.21 mg/mg has been regarded as abnormal and suggestive of HC[3,4]. Although the upper limits for UCa/Cr ratio are known for older children, these values are not well established in newborns. Interpretation of UCa/Cr ratios in neonates and infants less than three months of age should be evaluated with caution because such ratios have been shown to depend on both gestational age and source of milk protein (commercial formula versus human milk). Only a few studies of the urinary excretion of Ca, Na, and K, as assessed by their Cr ratios, have been performed in neonates[5,6]. Furthermore, no study has been conducted to establish upper limits for urinary sodium/creatinine (UNa/Cr) and urinary potassium/creatinine (Uk/Cr) values in neonates in our country. It is important to determine reference values of UCa/Cr for children at different ages in a given geographic area for early and correct diagnosis and for appropriate treatment to prevent calcium-containing renal stones in children, which is endemic in Turkey.

The purpose of this study was to determine the age-specific reference values for UCa/Cr in healthy neonates aged 0-28 days, and to evaluate the relationship between UCa/Cr, UNa/Cr, UK/Cr, and UNa/UK ratios in the same group. To further substantiate these differences related to age, we studied urinary Ca, Na and K excretion in the early and late newborn periods.

Material and Methods

Eighty-eight infants born in the Obstetric and Gynecology Department and followed up at the Newborn Department and Well-Child Clinics were enrolled in the study. Infants were eligible for the study if their birth weight was >3000 g, gestational age >37 weeks, and if they had no major chronic illness, kidney disorders, orthopedic problems, cardiac anomalies, respiratory distress syndrome or acidosis. Infants receiving either diuretic and/or dexamethasone therapy or parenteral nutrition and those with additional and specific need for calcium phosphate supplementation were excluded from the study. Since all children were breast-fed, no attempt was made to quantify dietary sodium, potassium, calcium, and fluid intake in any of the patients. None of the infants were receiving vitamin supplements at the time of the study. Adhesive urine collection bags were attached by nurses preparing the child for the visit. Non-fasting urine samples were collected between 9_{AM}-12_{PM}. If any infant was unable to give urine samples during the hospital visit, parents were requested to collect the urine at home and bring it to the hospital soon after voiding. Urine Na and K were studied in fresh voided urine samples by the same technician at the Biochemistry Department, whereas Ca and Cr were studied from frozen samples within one month. The urinary Ca levels were measured manually by the chlorinic acid method on the spectrophotometry at the Research Laboratory of the Pediatric Nephrology Department by the same technician. Two urine samples from the same child on consecutive days after the first daily feeding were collected and the mean values were obtained; these mean values were then compared with the first and second urine samples. The 95th percentile for UCa/Cr was estimated as the upper limit for HC. The ratios of UNa/Cr (mEq/mg), UK/Cr (mEq/mg), UCa/Cr (mg/mg) and UNa/UK (mEq/mEq) were calculated for each subject. Informed consent was obtained from parents to collect random urine samples.

Statistical Method

Analyses were performed using SPSS 9.0 program. The first and second urine samples and the differences between two groups were compared by Mann-Whitney U test. The correlations between parameters were determined by Spearmans correlation test. Results were considered statistically significant when $p < 0.05$. Data are presented as mean±standard deviation.

Results

A total of 88 infants (36 M, 52 F) were enrolled in the study. Subjects were divided into two groups according to their age: Group I: infants ≤7 days old (20 M, 35 F); Group 2: infants between 8-28 days old (16 M, 17 F). The distribution of boys/girls was similar in both groups. The median age of infants in Group I was two days and of infants in Group 2 was 17 days. The determination of urine Na and K was not performed in all samples because of insufficient urine samples. Urine Na and K analysis was performed in 68 and 76 neonates, respectively. When we compared the average UCa/Cr, UNa/Cr, UK/Cr, and UNa/UK values of the first and second urine samples with the values obtained from first and second urine samples, no statistical differences were found. There were no statistically significant differences in UCa/Cr, UNa/Cr, and UK/Cr ratios between girls and boys.

The UCa/Cr, UNa/Cr, and UK/Cr ratios in early newborn period were lower than in the late newborn period ($p < 0.001$, $p < 0.0001$, $p < 0.0001$, respectively).

The average of the mean values of the first and second urine samples and the 10th, 25th, 50th, 75th, 90th and 95th percentiles of the UCa/Cr, UNa/Cr, UK/Cr, and UNa/Uk in the early and late neonatal periods are shown in Table I. The frequency distribution of the UCa/Cr in each age group is shown in Figure 1. The data showed positive correlation between UCa/Cr and age ($r=0.38$, $p < 0.001$) as well as between age and UNa/Cr ratio ($r=0.68$, $p=0.0001$) and between age and UK/Cr ratio ($r=0.57$,

p<0.0001) (Figs. 2-4). A positive correlation was observed between UCa/Cr and UNa/Cr (r=0.613, p<0.0001) and UCa/Cr and UK/Cr (r=0.682, p<0.0001) (Figs. 5, 6). We also found a positive correlation between UNa/Cr and UK/Cr (r=0.61, p<0.0001) (Fig. 7). There was no statistically significant correlation between UCa/Cr and UNa/UK ratios. On the other hand, a positive correlation was observed between UNa/Cr and Una/Uk (r=0.61, p=0.0001) (Fig. 8). Mean urinary creatinine was higher (65.11±51.9) in the early newborn period when compared to the late newborn period (35.77±44) (p<0.01).

Table I. The Average of the Mean Values of the First and Second Urine Samples and the 10th, 25th, 50th, 75th, 90th and 95th Percentiles of the Uca/UCr, Una/Cr, UK/Cr, Una/UK in the Early and Late Neonatal Periods

	N	Mean	SD	Percentiles						95th CI
				10	25	50	75	90	95	
UCa/UCr										
≤7 days	55	0.11	0.10	0.03	0.05	0.07	0.14	0.28	0.36	0.08-0.14
8-28 days	33	0.27	0.23	0.03	0.08	0.2	0.40	0.68	0.79	0.19-0.36
UNa/Cr										
≤7 days	42	1.29	1.63	0.08	0.26	0.8	0.14	1.56	6.1	079-1.80
7-28 days	26	5.5	4.83	0.93	2.27	4.3	6.6	13.25	19.7	3.5-7.4
UK/Cr										
≤7 days	46	0.94	0.99	0.22	0.44	0.65	0.11	1.56	1.7	0.65-1.24
8-28 days	30	2.82	2.3	0.26	0.91	2.3	4.06	6.89	8.3	1.96-3.6
UNa/UK										
≤7 days	41	1.48	1.46	0.27	0.50	0.91	0.11	3.1	4.4	1.02-1.94
8-28 days	24	2.1	1.5	0.7	1.9	2.5	3.83	4.69	6.18	2.15-3.4

UCa: urinary calcium; UCr: urinary creatinine; UNa: urinary sodium; UK: urinary potassium; CI: confidence interval.
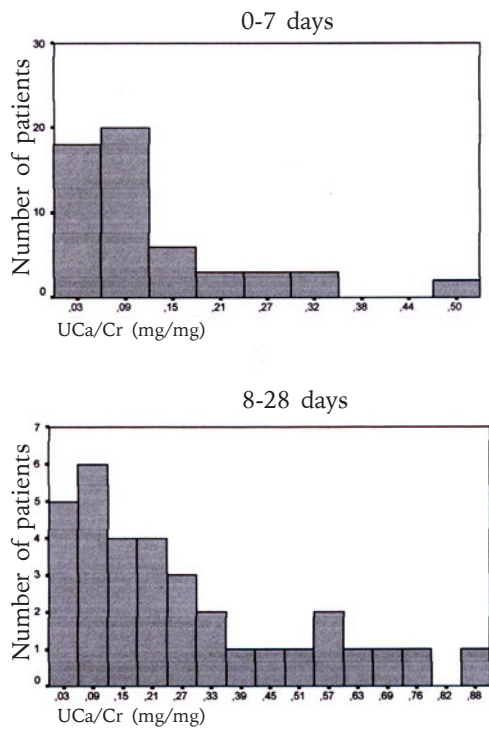

Fig. 1. The distribution of urinary calcium/creatinine (UCa/Cr) ratios in early and late newborn periods according to age.
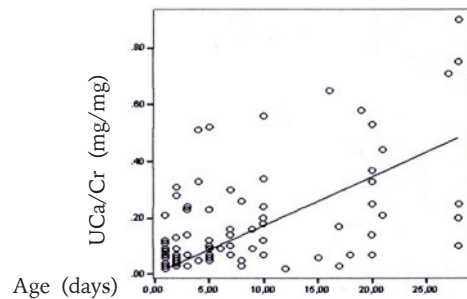

Fig. 2. Correlation between urinary calcium/creatinine (UCa/Cr) and age in neonates aged 0-28 days.
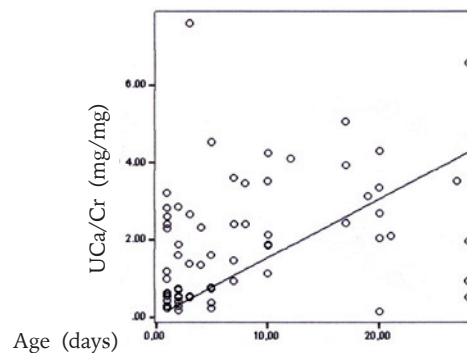

Fig. 3. Correlation between urinary sodium/creatinine (UNa/Cr) and age in neonates aged 0-28 days (r=0.68, p=0.0001).
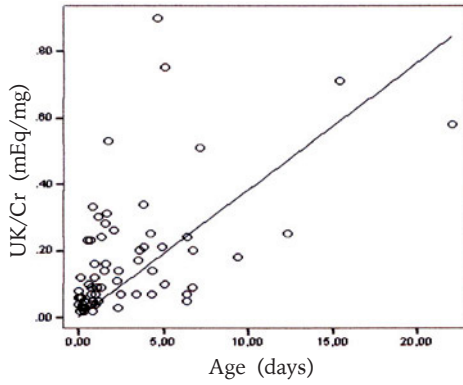
Fig. 4. Correlation between urinary potassium/creatinine (UK/Cr) and age in neonates aged 0-28 days   (r=0.68, p=0.0001).
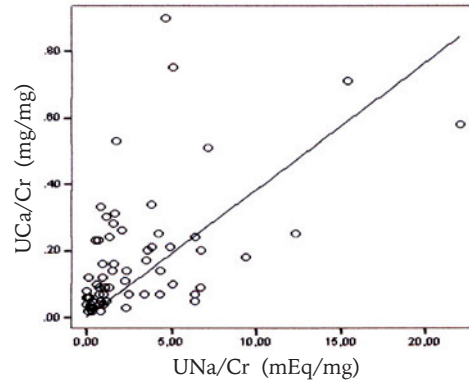

Fig. 5. Correlation between urinary calcium/creatinine (UCa/Cr) and urinary sodium/creatinine (UNa/Cr) in neonates aged 0-28 days (r=0.613, p<0.0001).

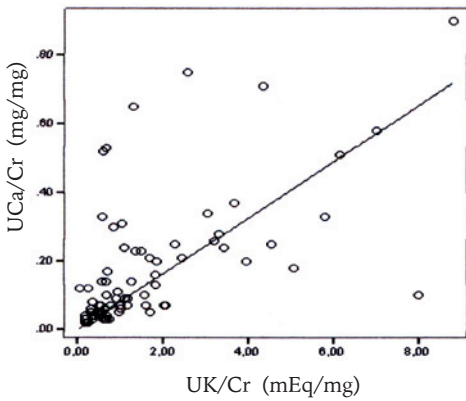
Fig. 6. Correlation between urinary calcium/creatinine (UCa/Cr) and urinary potassium/creatinine (UK/Cr) in neonates aged 0-28 days (r=0.682, p<0.0001).
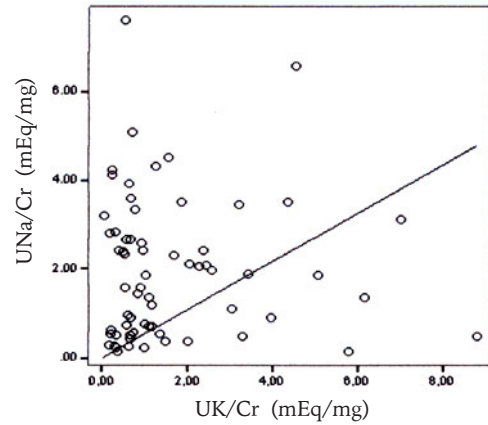

Fig. 7. Correlation between urinary sodium/creatinine (UNa/Cr) and urinary potassium/creatinine (UK/Cr) in neonates aged 0-28 days (r=0.61, p=0.001).
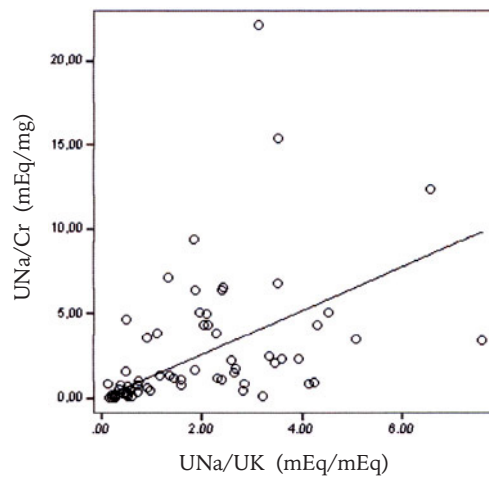

Fig. 8. Correlation between urinary sodium/creatinine (UNa/Cr) and urinary sodium/potassium (UNa/UK) in neonates aged 0-28 days (r=0.61, p=0.0001).

Discussion

Determination of urinary excretion of various substances in relation to the concentration of Cr in urine has been used as a reliable estimate in children for over 25 years since it excludes the need for timed urine sampling in children and offers simplicity and greater reliability. Moore et al.[7] first proposed the use of spot UCa/Cr ratio to screen for HC in children. Non-fasting urine samples have been used in many studies performed for the determination of the normal and upper levels of UCa/Cr[1,2,8]. Also, Trotter et al.[9] previously reported that there was no variation in the 24-hour circadian rhythm of Ca, Na and K excretion in newborns. All ratios in our study represented morning urine specimens. Some authors recommended that an average of at least two urine samples should be accepted as the UCa/Cr level because of the variations in the spot urine, whereas others have shown that only one second-morning urine sample was sufficient reliable enough to determine the UCa/Cr level because of the difficulties and high cost of obtaining more than one urine sample from children[1,8,10,11].

In our study, two urine samples from the same child on consecutive days were first collected and the average values of the two samples were determined. We then compared these average values with the first and second urine samples. We found no statistically significant difference between the average values and either sample. Our observation was that only one urine sample was sufficient for reliability and was representative in determining the random UCa/Ucr values (p>0.05). However, a 24-hr urine analysis should be performed to confirm the diagnosis of HC in children whose UCa/Cr ratio exceeds the 95th percentile in one urine sample and who have positive family history or nephrocalcinosis.

Few data are available on UCa excretion in infants[1,9]. As there is no data about the UCa/Cr ratio of infants 0-7 days old and 8-28 days old in the literature, no exact comparisons could be made. Moore et al.[7] defined HC in newborns as a Ca/Cr ratio higher than 0.18 mg/mg. In the present study, the mean UCa/Cr in the first 7 days of life was 0.11±0.10, similar to data obtained by César et al.[5] in newborns aged between 0-7 days. We found that the mean UCa/Cr ratio was 0.27 mg/mg in infants aged 8-28 days. This ratio was substantially higher than 0.1 mg/mg found in infants aged 1-7 days old. Sargent et al.[1] found a Ca/Cr ratio of 0.24 mg/mg in infants aged 5 days-7 months old. The difference in the UCa/Cr ratio between our study and the others is likely due to the difference in the age groups. In addition, gender, social and economic conditions, race and geographic characteristics are all important variables that can influence the UCa/Cr ratios. Previously, some articles alluded to an inverse relationship between UCa/Cr and age[1,2,12,13]. A positive correlation of UCa/Cr with age was found in our study and that ratio increased through the eight days of life. César P et al.[5] suggested the effect of consuming a large amount of milk and dairy products on higher UCa/Cr levels in infancy. All the infants in the study were breast-fed and none were receiving formula, cow's milk, vitamin D or calcium, potassium, or sodium supplementation, so the difference in Ca/Cr ratios between the early and late neonatal periods cannot be explained by these factors. When urinary creatinine levels were compared in the two groups, it was found that UCr was significantly higher in the first week of life (p<0.001). The literature is not entirely consistent with respect to changes in UCr excretion with age. De Santo et al.[14] showed that creatinine excretion is higher in young children versus older children, but no data about infants were reported. In a report by Feldman[15], it was stated that maternal Cr does influence both plasma and urinary Cr during the first week of life in healthy children, but probably not between the 15th and 30th days of life, whereas Matos et al.[16] demonstrated that the immaturity of the neonate tubule resulted in a reabsorption of Cr and a decrease in urinary excretion of Cr. The high urinary Cr levels in the early newborn period in our study may have been due to the effect of maternal Cr; the high Cr excretion in the early newborn period is likely to lower the UCa/Cr ratio. The majority of the studies on UCa/Cr excretion showed no differences between genders[1,10]), whereas Manz et al.[17] reported higher UCa/Cr values in boys than girls. No differences in the UCa/Cr ratios between girls and boys were found in the present study (p>0.05).

Sodium intake is one of the main factors influencing urinary excretion of Ca. Cirillo et al.[18] demonstrated that high Na and/or low K

excretion, which caused a high random UNa/UK ratio, was a high risk factor in developing urinary stone disease in adults. Osorio et al.[19] found a direct correlation between UNa/UK and UCa/Cr ratios, indicating the role of UNa and UK on the UCa/Cr ratio in HC children. They further reported that increased potassium intake in these children by either diet or medication led to a beneficial effect on the UCa/Cr ratio. As described by Cirillo et al.[18] and Osorio et al.[19], the association observed between urinary Na/K ratio and urinary stone disease can be accounted for by several mechanisms. Dietary sodium restriction reduces urine Ca excretion by reducing glomerular filtration rate (GFR) and increasing distal Ca reabsorption[7,18]. It is suggested that with increased salt intake, the coupling of UNa and UCa excretion results in an increase in UCa excretion. This leads to a decrease in serum calcium concentration, stimulating increased secretion of parathyroid hormone and consequently, of calcitriol[12]. Salt restriction has also been shown to be effective in reducing Ca excretion in patients with idiopathic HC. Our data showed that UNa/Cr also correlated positively with UCa/Cr (r=0.68, p=0.0001) in healthy neonates. The positive relation between UCa/Cr and UNa/Cr can carry some risks for higher Ca/Cr ratios in infants fed with commercial formula, which has higher Na content than human milk. As all the neonates in the present study were breast-fed, we were not able to compare the UNa/Cr and UK/Cr ratios to those of neonates fed with commercial formula. Similarly, we observed that UK/Cr ratios were lower in the first seven days of life when compared to the late newborn period (p<0.001). Unlike adults who are in zero balance, growing infants maintain a state of positive K balance. The relative conservation of K early in life is generally associated with higher plasma potassium values than in adults. The renal clearance of potassium in the infant is less than in the older child, even when corrected for GFR[20]. Plasma aldosterone concentrations in the fetus and newborn are high compared to those in the adult; yet clearance studies demonstrate a relative insensivity of the potassium secretory process to this hormone early in life[21]. Electrophysiologic analysis has confirmed the absence of functional potassium secretory channels in the luminal membrane of the neonatal collecting duct; these unique channels appear only after the second week of postnatal life, coincident with the appearance of K secretion in this segment[22]. The lower level of UK/Cr in the first days of life seen in our study can be explained by the lower excretion of K and higher excretion of Cr. It was interesting to observe a positive relationship between UK and UCa in the newborns, in contrast to the previous reports in adults and HC[19,23]. Rodriguez-Soriano[24] and Osorio[19] showed that HC children had decreased levels of fractional K excretion, suggesting that UCa concentration affects UK excretion. An increase in dietary potassium reduces UCa excretion, suggesting that K promotes renal Ca retention[23,24]. Contrary to these findings, we observed a positive correlation between UCa/Cr and UK/Cr ratios in neonates (r=0.682, p=0.000). It seems that the inverse relationship seen between UK/Cr and UCa/Cr in HC children is positive in healthy neonates. The normal UNa/UK ratio in children has been previously reported as higher than 2[24]. Ossorio et al.[19] reported that the mean UNa/UK ratios in children aged 4-18 years with voiding dysfunction was 2.28±1.31. In the present study, the mean UNa/UK was 1.48±1.46 in the first seven days of life and 2.1±1.5 in the late neonatal period (p>0.001). The 95th percentiles for UNa/UK in the early and late newborn periods were 4.4 and 6.18, respectively. There was a positive correlation between UNa/UK and age (r=0.4, p=0.001). Some reports showed that there was a linear correlation between UNa/UK and UCa/Cr ratios HC children and adults[19,25]. On the other hand, so et al.[2] reported that the relationship between UCa/Cr and UNa/UK in healthy children was extremely weak. They demonstrated that UNa/UK positively and strongly correlated with age: as the geometric mean of UCa/Cr decreased with advancing age, that of UNa/UK increased. They concluded that the linear relationship between Na/K and age could be due to the change in eating habits, since as children grew older, they consumed higher salt content meals. Similar to their findings, we did not observe a linear correlation between UNa/K and UCa/UCr ratios in healthy neonates, whereas a linear correlation between UNa/UK and age (r=0.40, p=0.001) was observed. It can be concluded that the linear correlation between UNa/UK

and UCa/Cr ratios reported in some previous studies might be due to the HC state of their patients. As none of our subjects were receiving formula, the effect of high Na content of formulas could be excluded as a determining factor on the relationship between age and UNa/UK.

In conclusion, in the present study we found that neonates in the first week of life have lower UCa/Cr, UNa/Cr, UKT/Cr, and UNa/UK ratios than those in the late newborn period. Whatever the reason for the positive correlation between UCa/Cr and age, it is not appropriate to use normal values for older children in the screening or monitoring of newborns. Contrary to the previous reports in hypercalciuric patients, our data suggest that healthy neonates differ from hypercalciuric patients by exhibiting a linear correlation between Na/K and UCa/Cr. However, more data on larger newborn groups are needed.

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