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ORIGINAL ARTICLE

Indications for cystography in children. Morphological abnormalities and functional defects

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Maximum urinary osmolality

Abstract
Objective: Until the introduction of ultrasound in clinical practice, routine performance of a cystography and urethrography was the standard of care following a first urinary tract infection (UTI). Current indications for this technique are based on clinical features, age or sex. This study aims to assess the importance of basic kidney function tests in determining the indication for cystography in the pediatric population.
Patients and methods: We conducted a cross-sectional observational and analytical, diagnostic accuracy study in 175 children who underwent ultrasound examinations for assessment of morphological abnormalities or with a history of one or more UTIs. We applied the term ''significant morphological abnormalities'' (SMAs) excluding cases with an anteroposterior diameter of the pelvis of less than 2 cm. The basic kidney function tests used in the assessment were the maximum urinary osmolality (UOsm) and urinary albumin/creatinine and NAG/creatinine ratios.
Results: The number of patients with normal cystography was 118; the remaining 57 had vesicoureteral reflux (VUR). We found a statistically significant association between UTI and VUR. Significant morphological abnormalities were present in 32/57 cases of VUR (56.1%) and the maximum UOsm was abnormal in 75% of cases with VUR (43/57). The association of ''UTI + significant SMA'' offered a negative predictive value (NPV) of 89% and a positive predictive value of 49%, leaving two cases of grade IV VUR undiagnosed. The association of UTI with ''SMAs or reduced maximum UOsm'' predicted all severe cases of VUR (grades IV-V).

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Conclusions: In children who have had UTI, in the presence of SMAs, prior determination of the maximum UOsm does not seem necessary to indicate a cystography. In patients who have not suffered from UTI, determining the maximum UOsm is useful for ruling out the presence of severe VUR. Renal tubular function tests, combined with other clinical, laboratory and sonographic variables, can guide decision-making to avoid unnecessary cystography.

PALABRAS CLAVE
Infección urinaria;
Anomalías morfológicas trascendentes;
Reflujo vesicoureteral;
Capacidad de concentración renal;
Osmolalidad urinaria máxima

Indicación de cistografía en la edad pediátrica. Anomalías morfológicas y defectos funcionales

Resumen
Objetivo: Hasta la introducción de la ecografía, era regla tras la primera infección de la vía urinaria (IVU), la indicación universal de una urografía y de una cistografía. Los criterios actuales habituales se limitan a aspectos clínicos, de edad o sexo. Este trabajo pretende valorar la importancia de las pruebas básicas de la función renal para precisar la indicación de cistografía en la población pediátrica.
Pacientes y métodos: Estudio unicéntrico observacional, analítico, de exactitud diagnóstica, con estructura transversal en el que se incluyeron 175 niños estudiados por anomalías morfológicas en la ecografía o por padecer una o más IVU. Se ha empleado el término «anomalías morfológicas trascendentes» (AMT) en el que no se incluyeron los casos con diámetro anteroposterior de la pelvis menor de 2 cm. Las pruebas básicas de función renal realizadas fueron la osmolalidad urinaria máxima (UOsm) y los cocientes urinarios albúmina/creatinina y NAG/creatinina.
Resultados: El número de pacientes con cistografía normal fue 118; tenían reflujo vesicoureteral (RVU) los 57 restantes. Se objetivó una asociación estadísticamente significativa entre IVU y RVU. En 32/57 casos de RVU (56,1%) existían AMT. La UOsm máxima fue anormal en el 75% de los casos con RVU (43/57). Con la asociación «IVU+AMT trascendentes» el valor predictivo negativo (VPN) fue del 89% y el valor predictivo positivo del 49%, quedando sin diagnosticar 2 casos de RVU grado IV. Con la asociación «AMT o UOsm máxima reducida» se diagnosticaron todos los RVU graves (grados IV-V).
Conclusiones: En los niños que han padecido IVU, si existen AMT no parece necesario determinar la UOsm máxima para indicar una cistografía. En los pacientes que no han padecido IVU la determinación de la UOsm máxima es útil para descartar la presencia de RVU grave. El estudio complementario de la función tubular renal junto a otras variables clínicas, analíticas y ecográficas, puede ayudar en la toma de decisiones que eviten realizar cistografías innecesarias.

Introduction

Changes in the management of urinary tract infections (UTIs) and patients with morphological abnormalities of the urinary system have been very uneven over time. Some have resulted from technical innovations, such as the introduction of prenatal or neonatal ultrasound examination of the urinary system. Until the introduction of ultrasound, the standard of care following a first UTI in children was routine performance of urethrography and cystography.[1] The advent of sonography brought on a partial change to existing imaging protocols, introducing the factor of age (urethrography and cystography in infants aged less than one year and ultrasound examination combined with radionuclide cystography from age 1 year).[2] Additional changes according to the sex of the patient were introduced soon after.[3]

In 2008, Isky Gordon et al. coined the term ''high-risk'' children in this context, that is, children at increased risk of vesicoureteral reflux (VUR), who would constitute the group in whom radiology or scintigraphy techniques would be indicated based on the findings of the ultrasound examination performed after an episode of febrile UTI. This introduced a new notion, that is, that there were children at ''low risk'' for VUR in whom, therefore, it would not be necessary to make extensive imaging assessments to screen for low-grade VUR.[4] In recent years, efforts have been made to establish criteria for the rational use of cystography,[5] especially since the long-held belief that UTIs could cause chronic kidney disease in the absence of renal morphological abnormalities has been dismissed.[6]

Past and recent recommendations from experts and working groups omit kidney function testing for ordering a

cystogram, except for a recent mention in the Spanish *Clinical Practice Guidelines on Urinary Tract Infections in the Pediatric Population*.[7] In this context, we conducted a study to assess the importance of performing tests to assess kidney function, especially in relation to fluid and electrolyte balance, to determine the indication of cystography in the pediatric population.

Sample and methods

Study design

We conducted a single-center cross-sectional diagnostic accuracy study in a sample of 175 pediatric patients (117 male; 58 female) aged 0–14 years referred to the outpatient clinics of our hospital due to the detection of morphological abnormalities in the prenatal or neonatal ultrasound examination or a history of one or more episodes of UTI. We collected data in winter 2023 and spring 2024 for patients who had been assessed at the hospital starting 3 years earlier. None of the cases had to be excluded due to known chronic kidney disease.

In our hospital, the imaging test introduced years ago to detect VUR has been contrast-enhanced voiding urosonography. All patients in the sample underwent this test; although, in this article, we use the classic term *cystography*. The severity of VUR was graded according to the classification of the International Reflux Study Committee (grades I–V).[8] The same grading scheme, based on equivalent criteria, is applied in voiding urosonography.[9] Depending on the established severity of VUR, we classified cases into 3 subgroups: mild (VUR grades I and II), moderate (grade III) and severe (grades IV and V). If VUR was bilateral, we used the higher grade for the analysis. *Hydronephrosis* was defined as an anteroposterior diameter (APD) of the renal pelvis equal or greater than 2 cm. Renal scintigraphy with ^{99m}Tc-dimercaptosuccinic acid (DMSA) was performed in 72 children at the time of diagnosis and in 80 by the end of follow-up, and all patients with UTI or clinically significant VUR were assessed with this technique. In patients with a prenatal diagnosis of hydronephrosis, antibiotic prophylaxis was initiated at birth.

Based on the findings of sonography and scintigraphy, we defined the variable ''significant morphological abnormalities'' (SMAs), which included renal scarring, renal hypoplasia, atrophic kidney, hydronephrosis, duplex kidney or ureteral dilatation on ultrasound (unmeasured). We also documented the cases in which any of these malformations were associated with an APD of less than 2 cm (Table 1).

We collected the renal function test results closest to the performance of cystography at diagnosis. However, the renal function tests were performed at least 4 months after the resolution of an episode of acute pyelonephritis. We did not take into account the findings of ultrasound scans performed in the first week of life on account of the potential for false negatives, since, due to the physiological reduction in renal glomerular filtration rate (GFR) at that stage, they may fail to identify urinary tract dilation.

Inclusion criteria

Age less than 14 years and documentation in the health records of at least one cystography, one renal ultrasound examination and one measurement of the maximum urinary osmolality (UOsm). When available, we also retrieved the values of the albumin/creatinine (n = 159) and N-acetylglucosaminidase (NAG)/creatinine (n = 123) ratios obtained from a first morning urine sample.

Exclusion criteria

We excluded patients aged more than 14 years with VUR and patients of any age with a diagnosis of multicystic dysplastic kidney, ureteropelvic or vesicoureteral junction obstruction, posterior urethral valves, or neurogenic bladder.

Urine concentration test with desmopressin (DDAVP)

Infants aged 0–12 months received an intranasal 10 μg dose of desmopressin in the morning and bottle feedings were restricted to half the usual volume through 6 PM to reduce the risk of water intoxication. Children aged 1–2 years received 20 μg of desmopressin via the intranasal route, with the same feeding restrictions. From age 2 years, patients received 0.12 mg (120 μg) of the oral lyophilizate formulation (DDAVP Melt), which dissolves instantly in the mouth. We collected the urine volumes excreted in the three subsequent bladder voidings which, in the case of continent children, were scheduled at 90 min intervals. From age 2 years, fluid intake was moderately restricted. The highest osmolality value was taken as the test result.[10,11]

Laboratory methods

Creatinine levels were determined with the creatininase method using a Modular Analytics automated analyzer (Roche/Hitachi; Mannheim, Germany). Albumin was measured using a nephelometric technique (Array), and NAG activity was determined using an enzymatic colorimetric assay based on the hydrolysis of 3-cresolsulfonphthaleinyl-*N*-acetyl-β-D-glucosaminide (Roche). Urine osmolality was measured using freezing point depression with an Osmostat osmometer (Menarini Diagnostics).

Reference values

The reference values used to define the normal range of the maximum UOsm following the administration of desmopressin were obtained in 125 healthy infants and published in a previous report by our research group.[10] Thus, the 5th percentile for the maximum UOsm is 532 mOsm/kg in infants aged 1–3 months; 616 mOsm/kg in infants aged 3–6 months, 645 mOsm/kg in infants aged 6–9 months and 740 mOsm/kg in infants aged 9–12 months. In children aged more than 1 year, the lower limit of normal is 800 mOsm/kg.[11] The normal ranges for age used for reference for the albu-

Table 1 Morphological findings in relation to cystography results.

	VUR (n = 57)	No VUR (n = 118)
Normal findings	6	10
Renal pelvis APD < 2 cm	19	87
Hydronephrosis	*6*	*7*
Unilateral scarring	*3*	*4*
Atrophic kidney + renal pelvis APD < 2 cm	*6*	*1*
Ureteral dilation + renal pelvis APD < 2 cm	*2*	*4*
Duplex kidney + renal pelvis APD < 2 cm	*3*	*2*
Atrophic kidney	*4*	*0*
Hydronephrosis + atrophic kidney	*4*	*0*
Renal scarring + renal pelvis APD < 2 cm	*1*	*1*
Renal hypoplasia + hydronephrosis	*0*	*1*
Renal hypoplasia	*1*	*0*
Renal hypoplasia + scarring	*1*	*0*
Hydronephrosis + renal scarring	*0*	*1*
Duplex kidney + ureterocele + renal pelvis APD < 2 cm	*1*	*0*

Significant morphological abnormalities are italicized (n = 53).
Abbreviations: APD, anteroposterior diameter; VUR, vesicoureteral reflux.

min/creatinine and NAG/creatinine ratios were reported in a previous publication.[12]

Statistical analysis

In the case of qualitative variables, we used the χ^2 test to compare two proportions, using the Yates correction as applicable. We did not perform tests to compare quantitative variables because the normal ranges varied with age. For the different parameters under study, we calculated the sensitivity, specificity, positive and negative predictive values (PPV, NPV) and positive and negative likelihood ratios (LR+, LR−) and the odds ratio (OR) for the detection of VUR. We considered *P* values of less than .05 statistically significant. The analyses were carried out with the statistical package SPSS version 20.0 (SPSS Inc, USA).

Results

General results

The sample included 117 boys (66.9%) and 58 girls. The number of patients with a normal cystography was 118 (83 male, 35 female) and the number of patients with VUR was 57 (34 male, 23 female). The first cystography was performed at a mean (SD) age of 12.74 (17.63) months (range, 0.20–97.5). In the group of 57 patients with abnormal cystography results, mild VUR was least frequent (n = 7), while moderate VUR was diagnosed in 23 children and severe VUR in 27 children.

Urinary tract infection

One or more episodes of UTI were diagnosed in 80 patients out of the total of 168 for whom data were available. The frequency of UTI diagnosis before the performance of cystography in absence of VUR was 40/115 (34.8%) compared to 40/53 (75.5%) in presence of VUR. No episodes of UTI were detected in 75 cases without VUR and in 13 cases with VUR. We found a statistically significant association between UTI and VUR (OR, 5.77 [95% CI, 2.77–12.02; *P* < .0001]; LR+, 2.07 [95% CI, 1.53–2.8]; LR−, 0.45 [95% CI, 0.29−0.69]).

We did not find differences in the number of diagnosed episodes of UTI (1, 2, or more than 2) based on the presence or absence of VUR, so in the subsequent statistical analysis we only used the variable ''urinary tract infection''.

Morphological findings and VUR. Significant morphological abnormalities

In 97 of the 118 cases with normal cystography (82.2%) the renal ultrasound and DMSA scans were normal or found a renal pelvis APD of less than 2 cm. On the other hand, in 32 of the 57 cases of VUR (56.1%) imaging found evidence of SMAs (OR, 5.91 [95% CI, 2.92–11.96; *P* < .0001]; LR+, 3.15 [95% CI, 2.01–4.95]; LR−, 0.53 [95% CI, 0.39−0.73]).

Table 1 presents the morphological findings according to the presence or absence of VUR.

Maximum urine osmolality and tubular function markers in relation the presence or absence of VUR

The mean (SD) age at the time of the urine concentration test was 10.46 (20.53) months (range, 0.03–160.73). The maximum UOsm was in the normal range in 72 of the 118 patients without evidence of VUR (61%).

The maximum UOsm was below normal in 75% of patients with VUR (43/57) (OR, 4.81 [95% CI, 2.37−9.75; *P* < .0001]; LR+, 1.94 [95% CI, 1.48–2.53]; LR−, 0.4 [95% CI, 0.25−0.65]) (Table 2). None of the patients with severe VUR (grades IV and V) had a maximum UOsm in the normal range. There were 14 patients with VUR who had a normal maximum UOsm (grade I, n = 2; grade II; n = 1; grade III, n = 11). Most of the children without VUR who exhibited urine concentrat-

Table 2 Association between the presence or absence of VUR and renal concentrating capacity.

	No VUR (n = 118)	VUR (n = 57)	
Normal maximum urine osmolality	72 (61%)	14 (25%)	
Reduced maximum urine osmolality		46 (39%)[a]	43 (75%)

Abbreviation: APD, anteroposterior diameter; VUR, vesicoureteral reflux.
[a] Renal pelvis APD < 2 cm, isolated (n = 35) or with unilateral dilation (n = 1); renal pelvis APD > 2 cm, isolated (n = 5) or with associated renal scarring (n = 1); normal morphology (n = 3); unilateral scarring (n = 1).

ing defects had lower urinary tract dilation (n = 36) or an APD greater than 2 cm (n = 6) (Table 2).

The albumin/creatinine ratio was in the normal range in 91 patients. It was also in the normal range in 39 patients with VUR. This ratio was elevated in 13 children with VUR and in 16 with normal cystography findings (OR, 1.89; *P* = .13).

The NAG/creatinine ratio was elevated in 13 out of 26 patients with VUR (33.3%) and in 16 of the 84 without VUR (19%) (OR, 2.13; *P* = .08).

Maximum urine osmolality, frequency of UTI and morphological findings in relation to VUR grade

The frequency of urine concentrating defects (43/57; 75.4%) and SMAs (32/57; 56.1%) increased with the grade of VUR. The distribution of UTIs (40/57; 70.2%) was different, more uniform in relation to VUR grades, with the exception of grade V, and may have been related to the use of antibiotic prophylaxis, although the sample size was small (Table 3).

Association of different variables with normal and abnormal urine concentrating capacity

These data are summarized in Table 4. Of the 89 patients with maximum UOsm values below normal, 46 had normal cystography findings and the remaining 43 had cystography findings indicative of VUR. Among the former, 8/89 had normal ultrasound findings, 49/89 a renal pelvis APD of less than 2 cm, and the rest (32/89) had SMAs. In this group of patients with reduced maximum UOsm values, we found a higher frequency of not only VUR, but also UTI diagnosis, in addition to increased NAG excretion in urine.

Measures of diagnostic accuracy for the combination of different variables

We calculated measures of diagnostic accuracy for prediction of VUR in the overall sample. The best results were achieved with the combination of two or three of the variables under study (Table 5).

Independently of whether they had experienced one or more UTI episodes, the combination ''SMAs or a reduced maximum UOsm'' (n = 112) exhibited the highest sensitivity (89.47%), with an NPV of 90.47% (LR+, 1.73 [95% CI, 1.42–2.11]; LR−, 0.22 [95% CI, 0.1−0.48]). This combination identified 51 of the 57 children with VUR (Table 6); the remaining 6 children with VUR, that is, those without SMAs and a normal UOsm, corresponded to one case of grade I, one of grade II, and four of grade III VUR (three with renal pelvis APD < 2 cm, two with one episode of UTI and a renal pelvis < 2 cm, and a sixth patient who had more than one UTI).

The combination ''UTI or SMAs'' achieved very similar values compared to the previous combination, but applying it would miss two cases of grade IV VUR, in addition to 2 cases of grade I/II VUR and three of grade III VUR (LR+, 1.99 [95% CI, 1.59–2.49]; LR−, 0.22 [95% CI, 0.11−0.45]).

The combination ''UTI or SMAs or reduced maximum UOsm'' achieved a slightly better NPV (93.3%). This combination identified 54 out of 57 cases of VUR, missing one case of grade I VUR and two cases of grade III VUR (LR+, 1.47 [95% CI, 1.27–1.71]; LR−, 0.15 [95% CI, 0.05−0.46]).

Discussion

This study included both patients with morphological abnormalities detected in the prenatal or neonatal ultrasound as well as those who had had one or more episodes of UTI. These are the two main reasons why cystography is usually ordered in everyday clinical practice.

In agreement with what has been known for some time, our series showed a clear association between UTI and VUR. However, it should be noted that half of the UTIs were diagnosed in the absence of VUR.

We did not find an evident association between VUR and renal pelvis dilation with an APD of less than 2 cm (Tables 1 and 3). It is known that mild/moderate dilation is not sufficiently sensitive to suspect VUR,[13,14] even applying the new, currently used system for the classification of what used to be known as renal ectasia (Urinary Tract Dilation [UTD] classification system).[14,15] In consequence, we did not include cases of renal pelvis dilation with an APD of less than 2 cm in the SMA subgroup. The recommendation in past articles to perform cystography in every case of urinary tract dilation appears to be obsolete.[16]

We propose the concept of SMA confirmed by renal ultrasound or scintigraphy (DMSA scan) (Table 1). The prevalence of SMAs increased in relation to the severity of VUR, from 28.6% in cases of mild VUR to 100% in cases of grade V VUR (Table 3). The presence of these anomalies was significantly associated with the presence of VUR (OR, 5.91; *P* < .0001).

With regard to renal function, we did not measure laboratory markers that require blood collection to assess glomerular renal function, such as creatinine or cystatin C. These markers are highly specific for kidney injury but offer a very low sensitivity, and by the time abnormal values are found, the reduction in functioning renal parenchyma is considerable. We measured three functional markers of

Table 3 Morphological and functional findings in relation to the grade of vesicoureteral reflux (n = 57).

	One or more UTIs (n = 40)	Urine concentrating defect (n = 43)	Significant morphological abnormalities (n = 32)	Renal pelvis APD < 2 cm (n = 17)
Mild VUR (n = 7)	5 (71.4%)	4 (57.1%)	2 (28.6%)	3 (42.8%)
Moderate VUR (n = 23)	16 (69.6%)	12 (52.2%)	11 (47.8%)	8 (34.8%)
Grade IV VUR (n = 18)	15 (83.3%)	18 (100%)	10 (55.5%)	6 (33.3%)
Grade V VUR (n = 9)	4 (44.4%)	9 (100%)	9 (100%)	

Abbreviation: APD, anteroposterior diameter; UTI, urinary tract infection; VUR, vesicoureteral reflux.

Table 4 Association of study variables with normal and abnormal renal concentrating capacity.

	Normal concentrating capacity (n = 86)	Urine concentrating defect (n = 89)	Odds ratio
Sex	56 M, 30 F	61 M, 28 F	
Urinary tract infection	No: 51/84	No: 37/84	1.96 (95% CI, 1.06—3.63), $P = .03$
	Yes: 33/84 (38.4%)	Yes: 47/84 (52.8%)	
APD < 2 cm	57/86 (66.3%)	49/89 (57%)	
Significant morphological abnormalities	21/86 (24.4%)	32/89 (36%)	
VUR	No VUR: 72/86	No VUR: 46/89	4.81 (95% CI, 2.37—9.75), $P < .0001$
	VUR: 14/86 (16.3%)	VUR: 43/89 (48.3%)	
Albumin/creatinine ratio	Normal: 65/76 Elevated: 11/76 (12.8%)	Normal: 65/83 Elevated: 18/83 (21.7%)	ns
NAG/creatinine ratio	Normal: 50/57	Normal: 44/61	2.76 (95% CI, 1.05—7.28, $P = .04$
	Elevated: 7/57 (12.3%)	Elevated: 17/61 (27.9%)	

Abbreviations: APD, anteroposterior diameter of the renal pelvis; F, female; M, male; NAG, N-acetylglucosaminidase; ns, not significant; VUR, vesicoureteral reflux.

Table 5 Diagnostic accuracy measures for prediction of VUR for different variable combinations.

	Sen	Spe	PPV	NPV	OR
Significant morphological abnormalities or reduced maximum UOsm (n = 112)	89.5%	48.3%	45.5%	90.5%	7.94 (95% CI, 3.17—19.92), $P < .0001$
UTI or significant morphological abnormalities (n = 102)	87.7%	55.9%	49.0%	90.4%	8.93 (95% CI, 3.74—21.33), $P < .0001$
UTI or significant morphological abnormalities or reduced maximum (n = 130)	41.5%	35.6%	41.5%	93.3%	9.94 (95% CI, 2.93—33.77), $P = .0002$

Abbreviations: NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; Sen, sensitivity; Spe, specificity; UOsm, maximum urine osmolality; UTI, urinary tract infection.

demonstrated utility for early detection of kidney injury that are also easy to measure in spot urine samples, the maximum UOsm and the albumin/creatinine and NAG/creatinine ratios. The last two were not significantly associated with the presence of VUR in our sample. On the other hand, we found normal maximum UOsm values in 61% of patients without evidence of VUR and abnormal values in 75% of patients with VUR (43/57) (Table 2). None of the children with severe VUR (grades IV and V) had a maximum UOsm in the normal range (Table 3). However, of the cases of moderate VUR, only 52% were associated with urine concentrating defects (Table 3), which constitutes a partial limitation to our conclusions, as some antibiotic prophylaxis could be beneficial in some of these cases depending on the circumstances.

The sensitivity of the urine concentration test for detection of kidney injury is higher compared to other markers because it is a global marker indicative of tubular integrity

Table 6 Patients with VUR (n = 51) who had significant morphological abnormalities or a reduced maximum urine osmolality.

	n	VUR grade	One or more UTIs
Significant morphological abnormalities and concentrating defect	24	9 grade V, 10 grade IV, 4 grade III, 1 grade I	15/24
Concentrating defect without significant morphological abnormalities	19	8 grade IV, 8 grade III, 3 grades I-II	17/19
Significant morphological abnormalities without concentrating defect	8	7 grade III, 1 grades I-II	5/8

Abbreviations: UOsm, maximum urine osmolality; UTI, urinary tract infection; VUR, vesicoureteral reflux.

when its results are normal, that is, it is not a marker of a specific tubule segment, but of the tubules overall, as normal results depend on the preserved handling of sodium and chloride in each functional segment, preserved structure and function of the medullary countercurrent mechanism, and normal water permeability of the tubules in response to vasopressin.[10,12]

The pathophysiological mechanism by which VUR results in a reduced maximum UOsm involves the additive effects of the increased pressure exerted on the renal parenchyma and the associated loss of nephron mass, which may be congenital or acquired.[17,18]

Our findings as well as previously published data demonstrate that changes in renal water handling are directly associated with the grade and severity of VUR.[10,19,20] Thus, the effects of increased pressure on renal function have been investigated in experimental models by producing ureteral obstruction, which translates to a reduction in the activity of some tubular sodium channels,[21,22] in the expression of urea transporters[23] and the activity of aquaporins expressed in the collecting ducts.[24] Specifically, one experimental study demonstrated the negative impact of VUR on the expression of aquaporins 1 and 2.[25]

Table 7 offers a summary of the articles published by our group, presenting the evidence gathered on the efficacy of basic renal function tests (maximum UOsm, albumin/creatinine and NAG/creatinine ratios) in common conditions characterized by the loss of renal parenchyma or increased pressure on the urinary tract.[10,12,26–30] As can be seen in the table, the urine concentrating capacity is the most sensitive marker of functional renal impairment in various conditions commonly encountered in pediatric care. The key issue investigated in the present, complementary study is whether the maximum UOsm can be a useful marker for the purpose of determining the indication of cystography.

Table 8 presents the indications for cystography published in recent years in various guidelines and articles.[7,31–36] The broader indications applied decades ago have been abandoned[1–3] and more specific indications are being pursued, chiefly aiming at the detection of high-grade VUR.[4,33] Recent criteria, while heterogeneous, tend to agree on the performance of cystography in the presence of severe morphological abnormalities detected by sonography or DMSA scintigraphy, in young male patients and in the case of recurrent febrile UTIs, especially when caused by bacteria other than *Escherichia coli*.[7,31–36] It is widely accepted that isolated renal pelvis dilation is not an indication for performing imaging tests beyond the ultrasound.[32]

It is remarkable that, both in the past and today, criteria such as age or clinical factors are taken into account to determine the indication for cystography, given the disparity and potential for confusion that this may entail in the selection of candidates, for example, in the case of a girl aged more than 2 or 3 years of age with a febrile UTI or cystitis caused by a bacterium other than *E coli*. However, the presence of morphological abnormalities is an identifiable and measurable criterion that is not as variable.

Table 8 reflects the omission of renal function testing in all articles, save for a passing and inexplicit mention in the recent Spanish guideline.[7]

The three predictor combinations presented in Table 5 had NPVs around 90%, that is, performed well as criteria to determine the indication of cystography that could prevent some unnecessary tests. The LR− obtained for isolated variables (0.53 for morphological abnormalities and 0.4 for the maximum UOsm) were superior to those obtained for the three combinations (0.22 in two of them and 0.15 in the other), although these values are considered moderate changes in the probability of ruling out VUR. The PPV of the three combinations ranged between 41.5% and 49%. The reason for this is that both morphological abnormalities on imaging and VUR can be present in the absence of a history of UTI, especially in children who have received antibiotic prophylaxis. Thus, the association of impaired urine concentrating capacity with morphological abnormalities or a relevant clinical history (UTI) improves diagnostic accuracy (with increases in the NPV and the odds ratio and a decrease in the LR−), although with a lesser specificity in the latter case which, therefore, would result in the performance of cystography in a larger number of patients.

On the other hand, many cases of mild or moderate urinary tract dilation that do not result in obstruction or are not associated with VUR do present with urine concentrating defects (Table 2). No hypothesis has been proposed as to the underlying mechanism of this association, although it may involve the functional immaturity of the renal medulla, with or without the presence of abnormally short loops of Henle. A longitudinal study conducted by our group identified a trend of progressive normalization over time.[37]

Applying the proposed eligibility criteria, none of the cases of severe VUR (grade IV-V) would have been missed if the maximum UOsm was included (Table 6). The combination ''SMAs or reduced maximum UOsm'' clearly simplifies the initial indication of cystography without needing to consider age, sex, or the location or causative agent of UTI. The other advantage of this simple criterion, as we already

Table 7 Articles published by our group demonstrating the efficacy of basic kidney function tests in common conditions encountered in everyday pediatric nephrology practice.

Title, journal, year and reference	Sample characteristics	Summary of results
Should a cystography be performed on all breastfeeding infants with mild to moderate dilatation of the urinary tract? Renal function tests can help to answer this question. Nefrología 2011[25]	79 infants (57 M, 22 F) with mild/moderate urinary tract dilation (0.5–2 cm diameter in the postnatal ultrasound)	Compared to infants without VUR (n = 68), infants with VUR (n = 11; 5 grade I–II, 5 grade III and 2 grade IV) had significantly lower maximum UOsm values and significantly higher microalbumin/creatinine and NAG/creatinine ratios
Diagnostic efficiency and quality indexes of several markers of renal function for detecting the loss of parenchyma in paediatric *patients.* Nefrología 2012[11]	179 patients (91 M, 88 F). Evidence of loss of renal parenchyma in 102 patients (57%) on the DMSA scan	Classifying patients according to the scintigraphy findings, we found significant differences between the two groups (normal vs abnormal DMSA scan) in maximum UOsm and the eGFR.
Water renal management is altered more frequently than albuminuria in children in the G1 stage of the 2012 KDIGO Guideline. Nefrología 2015[26]	116 children (64 M, 52 F). Included 100 patients with G1 stage and 16 with G2–G5 stage chronic kidney disease	In children with G1 stage disease (normal eGFR), abnormal values in markers related to renal water were more frequent than abnormal urinary albumin values
Renal tubular markers as screening tools for severe vesicoureteral reflux. Eur J Pediatr 2019[9]	163 children (111 M, 52 F) with a diagnosis of UTI. 100 patients with normal cystography, 36 with VUR grades I-III and 27 with severe VUR	Significant decrease in UOsm and increase in urinary NAG secretion with increasing VUR grade
Usefulness of basic renal function tests in the management of hydronephrosis. Cir Pediatr 2020[27]	38 children (30 M, 8 F) with hydronephrosis (renal pelvis $\geq$ 20 mm): 12 with ureteropelvic junction obstruction, 8 with high-grade VUR and 18 with non-obstructive hydronephrosis without VUR	No child with high-grade VUR had a normal UOsm. Cystography could have been avoided in 43% of patients with a normal UOsm without missing a single case of high-grade VUR
The use of urinary osmolality to evaluate postoperative renal function in children with ureteropelvic junction obstruction. J Pediatr Urol 2021[28]	56 children (33 M, 23 F) with unilateral ureteropelvic junction obstruction. Basic kidney function tests performed before and after surgery	The most sensitive parameter to detect alterations in renal function in children with ureteropelvic junction obstruction is the UOsm, which, therefore, is also the most useful in the postoperative follow-up
Reflux nephropathy and scarring nephropathy: So close and yet so different. An Pediatr 2022[29]	Longitudinal study in 89 children (46 M, 43 F) with diagnosis of VUR. Basic kidney function tests performed at diagnosis and after resolution of VUR	Urine concentrating defects are the most frequent finding in children with active VUR (true ''reflux nephropathy''), while the most common functional abnormality after VUR has been cured is an increased urinary albumin concentration. The term ''dysplastic-scarring nephropathy'' could be more appropriate for patients with residual morphological lesions and impaired renal function, once VUR is cured.

DMSA, renal scintigraphy performed with ^{99m}Tc-DMSA; eGFR, estimated glomerular filtration rate; F, female; M, male; NAG: N-acetylglucosaminidase; UOsm, urine osmolality; UTI, urinary tract infection; VUR, vesicoureteral reflux.

noted, is that it does not fail to identify any patients with severe VUR, who are ultimately those who require closer monitoring and possibly surgical intervention.[35,38]

Our study has the limitations intrinsic to its retrospective design, such as potential variation in the diagnosis of UTI, the fact that urinary albumin and NAG were not measured in all patients or the greater difficulty in interpreting the findings of contrast-enhanced voiding urosonography for reflux grading. In addition, also due to its retrospective nature, the fact that our group has been convinced for many years of the utility of measuring UOsm in everyday practice may have resulted in the decision not to perform cystography in

Table 8 Criteria for performance of cystography published in recent years.

Title, journal, year and reference	Indication for cystography
Reaffirmation of AAP Clinical Practice Guideline: The diagnosis and management of the initial urinary tract infection in febrile infants and young children 2–24 months of age. Pediatrics 2016[30]	Voiding cystourethrography should not be performed routinely after the first febrile UTI; it is indicated if the ultrasound scan reveals hydronephrosis, scarring, or other findings that would suggest either high-grade VUR or obstructive uropathy, as well as in other atypical or complex clinical circumstances. Further evaluation should be conducted if there is a recurrence of febrile UTI.
Updated Italian recommendations for the diagnosis, treatment and follow-up of the first febrile urinary tract infection in young children. Acta Paediatr 2020[31]	Cystography would be indicated after the first febrile UTI when the first renal and bladder ultrasound reveals unilateral or bilateral renal hypoplasia, anomalies of parenchymal echogenicity, ureteral dilatation, uroepithelial thickening of the renal pelvis and pelvicalyceal dilatation, particularly if associated with uroepithelial thickening, bladder abnormalities. In addition, imaging for the detection of VUR should be performed when the UTI is caused by a pathogen other than *E coli* and in children with recurrent febrile UTIs.
Update of the EAU/ESPU guidelines on urinary tract infections in children. J Pediatr Urol 2021[32]	It is important to diagnose high-grade VUR after the first UTI since this is an important risk factor for renal scarring. The most important risk factors for high-grade VUR and subsequent scarring are: abnormal renal ultrasound, high grade fever and non-*E coli* infections.
Urinary tract infection in under 16s: diagnosis and management. London: National Institute for Health and Care Excellence (NICE) 2022[33]	For babies aged less than 6 months, cystography would be indicated in the case of atypical or recurrent UTI; and could be considered in the case of abnormal ultrasound findings. In children aged 6 months to 3 years, cystography should be considered if the following features are present: dilatation of urinary tract on ultrasound, poor urine flow, non-*E coli* UTI or family history of VUR
Evidence-based clinical practice guideline for management of urinary tract infection and primary vesicoureteric reflux. Pediatr Nephrol 2024[34]	UTI caused by uropathogen other than *E coli* in children aged less than 2 years, abnormal ultrasound findings or history of recurrent UTI
Actualización de la guía de práctica clínica española sobre infección del tracto urinario en la población pediátrica. Síntesis de las recomendaciones sobre diagnóstico, tratamiento y seguimiento. An Pediatr (Barc) 2024[7]	Recurrent febrile UTI. Febrile UTI and family history of VUR. Febrile UTI with abnormal urine stream in boys or abdominal/vesical mass. Febrile UTI and abnormalities on ultrasound (except low-grade dilation) or on DMSA scan (except mild defects with no impact on renal function). The estimation of the GFR and, especially, measurement of the maximum UOsm, urinary albumin or urinary NAG can guide decision-making during the initial diagnosis and subsequent follow-up.
Prediction model for severe vesicoureteral reflux in children with urinary tract infection and/or hydronephrosis. Pediatr Nephrol 2025[35]	Age less than 2 years, male sex, growth of uropathogen other than *E coli*, presence of UTD-P3 dilation on ultrasound and multiple kidney scars on DMSA scintigraphy were associated with severe reflux.

Abbreviations: DMSA, renal scintigraphy with ^{99m}Tc-DMSA; eGFR, estimated glomerular filtration rate; NAG, N-acetylglucosaminidase; UOsm, maximum urine osmolality; UTD, Urinary Tract Dilation classification system; UTI, urinary tract infection; VUR, vesicoureteral reflux.

patients with a normal urine concentrating capacity, which could have affected our estimation of diagnostic accuracy.

In short, based on our findings, if SMAs are present in children with a previous history of UTI, measurement of the maximum UOsm would not be necessary to determine the indication of cystography. However, measurement of UOsm would slightly improve the NPV without missing any cases of grade IV VUR. In cases in which severe VUR needs to be ruled out in a patient without a history of UTI, a urine concentration test would be helpful. One of the drawbacks of the functional test that we propose is that urine concentrating capacity is preserved in nearly half of the patients with

moderate VUR, most likely because the increase in pressure is not significant, and, as we noted above, some of these patients could benefit from antibiotic prophylaxis. In any case, the performance of renal tubular function tests as a complement to other clinical, laboratory and sonographic variables can help guide decision-making and contribute to preventing the performance of unnecessary cystograms.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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