Assessment of Pediatric Hydronephrosis Using Output Efficiency

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Diagnosing obstruction in pediatric patients with hydronephrosis, and renal impairment is often difficult. Renal output efficiency (OE) is a parameter that may improve diagnostic accuracy by allowing normalization of washout according to renal function. The aims of this study were to define a normal range for OE in infants and children and to evaluate its diagnostic accuracy in cases with hydronephrosis. **Methods:** Seventy-four children (91 hydronephrotic kidneys; median age, 4 mo; 22 girls and 52 boys) underwent ^{99m}Tc-labeled mercaptoacetyl-triglycine scintigraphy using intravenous volume expansion (15 ml/kg normal saline), furosemide diuresis and urethral catheterization, if vesicoureteric reflux was present. Images were interpreted by consensus of two or more experienced observers using visual assessment of the images, differential function and clearance half-time after furosemide ($T\frac{1}{2}$), as well as OE. The final diagnosis was based on surgical findings (n = 23 kidneys) or follow-up for >12 mo (n = 68). **Results:** Final diagnosis in 22 of the 91 hydronephrotic kidneys was obstruction at the pelviureteric (n = 21) or vesicoureteric (n = 1) junction and no obstruction in the remaining 69. The overall diagnostic accuracy of OE was 89%. Using exhaustive search multivariate logistic regression analysis, only reduced OE ($p < 0.001$) and decreased renal uptake by visual assessment ($p = 0.058$) were independently predictive of obstruction ($R^2 = 0.726$). In dilated but unobstructed kidneys, mean OE was 93% ± 7.1%. In the normal kidneys, mean OE was 96% ± 3.1%. **Conclusion:** OE improves the diagnostic accuracy of diuretic renography in children and neonates with hydronephrosis and suspected obstruction. Output efficiency should exceed 89% in normal kidneys and 79% in unobstructed, hydronephrotic kidneys.

Key Words: hydronephrosis; output efficiency; pediatric

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Pediatric hydronephrosis (HN) often presents a management problem, particularly in neonates and children with impaired renal function. The natural history of neonatal and childhood HN is variable, with some spontaneously improving and others deteriorating and requiring surgery. Diagnostic algorithms generally include diuretic renography. Although popular, the radionuclide technique may be confounded by several factors, including the evolving nature of the condition, reduced renal function and marked pelvicalyceal dilatation.

The routine use of volume expansion (*1,2*) and newer radiopharmaceuticals such as ^{99m}Tc-labeled mercaptoacetyl-triglycine (^{99m}Tc-MAG3) (*3,4*) has helped reduce some of these test limitations. However, accurate stratification often remains difficult when conventional qualitative and quantitative scintigraphic criteria are used.

A more recently described parameter, output efficiency (OE), allows normalization of washout according to renal function. Initial data confirm that OE helps compensate for renal dysfunction and suggests a promising role in the evaluation of HN (*5,6*). Its value in children has not been widely reported.

Accordingly, the purposes of this study are to define a normal range for OE in the pediatric population and to assess the diagnostic accuracy in children with HN and suspected pelviureteric junction (PUJ) obstruction.

MATERIALS AND METHODS

We retrospectively reviewed the records of children referred with suspected PUJ obstruction over a 2.5-yr period who fulfilled the following criteria: OE and clearance $T\frac{1}{2}$ were available; there was no prior renal or ureteric surgery; and a final diagnosis based on surgical/histopathological findings or follow-up for at least 12 mo was available. Seventy-four children (91 HN kidneys) met these criteria and form the basis of this report. There were 22 girls and 52 boys. The median age was 4 mo (mean age, 1.5 yr; range, 3 wk–14.5 yr). There were 17 children with bilateral HN, 56 with unilateral HN and 1 child with a solitary kidney.

Histopathological confirmation of obstruction required a marked increase in collagen around and between smooth muscle cells in the obstructed segment (*7*). Final diagnosis in the nonsurgical group (n = 68 kidneys) was based on the referring physician's diagnosis using clinical judgment, repeat MAG3 renography (n = 27 patients), changes in the degree of HN on ultrasound (n = 14 patients) and/or percutaneous antegrade pyelogram (n = 1).

Our diuretic renographic protocol comprised volume expansion with oral fluids and 15 ml/kg of intravenous 0.9% sodium chloride over the 30 min preceding the test, followed by maintenance of intravenous fluids at 10 ml/kg/hr during the scan. Urinary bladder catheterization was not routinely performed for practical reasons unless vesicoureteric reflux was present or vesicoureteric junction obstruction was suspected. In this study, 14 patients (21 HN kidneys) were catheterized.

A ^{99m}Tc-MAG3 renal scan was then performed, with the dose adjusted for body weight based on an adult dose of 200 MBq. Sedation was not routinely used, but if required, oral midazolam (0.5 mg/kg) with paracetamol syrup (20 mg/kg) or alternatively chloral hydrate (50 mg/kg) was administered. In such circumstances, strict monitoring of the child's respiration and oxygenation was performed (pulse oximeter).

Posterior imaging with the patient in the supine position was performed using a large-field-of-view gamma camera and a low-energy, all-purpose, parallel-hole collimator interfaced to a Max-DELTA computer system. A continuous 40-min acquisition protocol with 40 1-sec frames, followed by 120 20-sec frames was used. Intravenous furosemide was administered at 20 min or when peak pelviureteric activity was assessed to be present in the images by the supervising physician. The furosemide dose was 1 mg/kg for infants <12 mo of age and 0.5 mg/kg for older children. Patients referred for progress scans received a dose at least equivalent to or usually greater than that in the previous study. An image, after gravity-assisted drainage (upright position) and voiding, was obtained and reported in conjunction with the other images to assess the degree of clearance from the collecting system.

The region of interest (ROI) used in calculating the OE and $T\frac{1}{2}$ encompassed both the kidney and dilated renal pelvis. The background ROIs used at this institution were separate semilunar ROIs, adjacent to the superior and inferior poles of the kidney. Although

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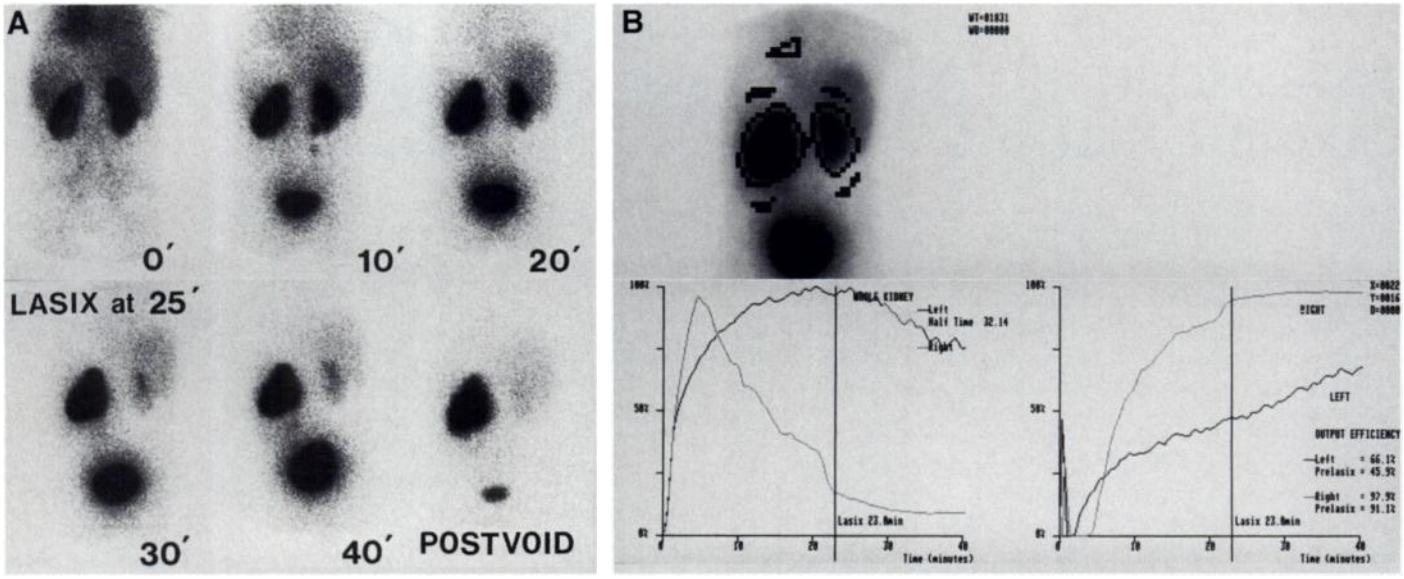

FIGURE 1. (A) Posterior ^{99m}Tc-MAG3 images of a 3.5-yr-old boy with left PUJ obstruction. (B) The ROI for OE calculation (upper left) encompasses the kidney and dilated collecting system. The generated renogram (lower left) and OE (lower right) curves span 0–40 min. The time of furosemide administration is indicated. The y-axis of the OE curve represents the OE (the integrated output expressed as a % of the integrated input), and the x-axis represents time. Both the postfurosemide $T\frac{1}{2}$ (32 min) and the total OE of the left kidney (~66%) are abnormal and consistent with obstruction. The right kidney has a normal OE of ~98%.

this method is more operator-dependent, it may allow a more representative background ROI to be selected than the less discriminating circumferential ROI. The $T\frac{1}{2}$ after furosemide was generated using a monoexponential curve fitted to the maximum slope of the diuretic curve. Visual assessment of uptake and washout (graded as normal or reduced) was recorded for each kidney. The differential renal function was calculated using the integral of the second phase of the background subtracted renogram curve.

OE was calculated for the duration of the study (0–40 min) for the HN kidneys (n = 91) and also for the normal kidneys with no HN (n = 56). In brief, background subtraction was performed on each whole kidney time–activity curve. The integral of the blood clearance curve obtained from a region over the left ventricle was fitted to a part of the second rising phase of the background-corrected kidney curve by an iterative least-squares technique. The resultant fitted curve corresponded to the integrated input to the kidney as a function of time. By subtraction of the background-corrected kidney curve from the integrated input, a curve representing the integrated output from the kidney was obtained. Output efficiency is the integrated output expressed as a percentage of the integrated input (*5*).

Each scan was classified by the consensus opinion of at least two experienced observers as obstructed, unobstructed or indeterminate by standard parameters. Obstruction was defined as the presence of two or more of the following: $T\frac{1}{2}$ >20 min; differential renal function ≤40%; and/or poor clearance from the pelvicalyceal system after furosemide or minimal renal function revealed by image assessment (Fig. 1). Kidneys were classified as unobstructed if at least two of the following were present: $T\frac{1}{2}$ ≤10 min; normal differential renal function; and/or image assessment revealed good clearance of ^{99m}Tc-MAG3 from the renal pelvis (Fig. 2). Patients not meeting these criteria were indeterminate for obstruction. The OE was not reported to the referring clinicians during the study period and therefore did not influence management decisions.

Because of technical difficulties in clearly separating the renal cortex from the adjacent collecting system in some kidneys, the renal parenchymal transit times were not included in our assessment.

Multivariate logistic regression analysis of clinical (sex and age) and scintigraphic (OE, $T\frac{1}{2}$, differential function, visual assessment of uptake and washout) covariables was undertaken to determine which factors predicted outcome (obstructed or unobstructed). Variance was defined using the most parsimonious model.

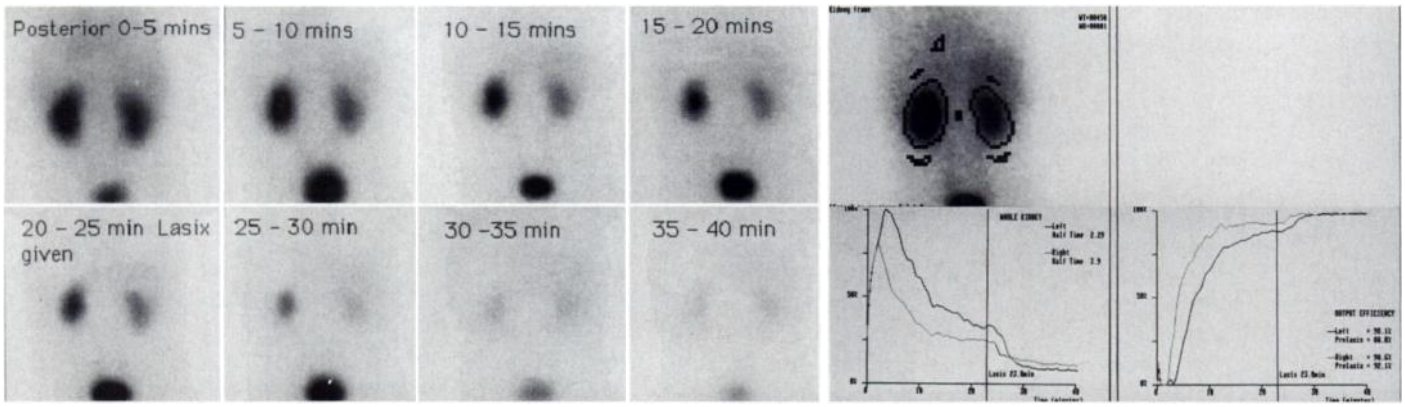

FIGURE 2. (A) Posterior ^{99m}Tc-MAG3 images of a 4.5-mo-old boy with an unobstructed, HN left kidney. (B) The renogram curve (lower left) reflects the prompt clearance from the left kidney with further clearance following furosemide. The postfurosemide $T\frac{1}{2}$ is normal at <3 min. The OE curve (lower right panel) demonstrates a normal OE exceeding 98% from both kidneys.

TABLE 1
Comparison of Diagnostic Value of Standard Criteria and OE

Final outcome	Detection by	
	Standard criteria*	OE
Obstructed (n = 22 kidneys)	19	20
Not obstructed (n = 69 kidneys)	52	61
Total (n = 91 kidneys)	71	81
Accuracy (%)	78	89

*Standard criteria are based on image assessment, differential renal function and diuretic washout $T\frac{1}{2}$.

TABLE 3
Utility of OE in Predicting Obstruction

Initial OE*	HN kidneys (n = 91)
True-positive†	20
True-negative†	61
False-positive†	8
False-negative†	2
Accuracy	89%

*OE <79% consistent with obstruction.
†Determined by surgical/histopathological findings or clinical follow-up.

RESULTS

The final diagnoses in the 91 HN kidneys were obstruction (n = 22) at the PUJ (n = 21) or vesicoureteric junction (n = 1) or no obstruction (n = 69). The final diagnosis was based on surgical/histopathological findings (n = 23) or follow-up (n = 68). Histopathology confirmed all cases of suspected obstruction. Normal histopathology was found in one patient (one kidney), who had been classified as unobstructed but underwent surgery for symptoms of recurrent urinary tract infection and pain.

The mean OE in the normal kidney (n = 56) of patients with contralateral HN was 96% ± 3.1%. A similar value (95% ± 3.5%) was found in the subgroup of children <6 mo in age. The mean OE in the dilated, unobstructed kidneys was 93% ± 7.1%. An OE value of <79% (based on 2 s.d. below this mean) was considered abnormal and consistent with obstruction.

Using standard criteria, the HN kidneys were classified as obstructed (n = 19), unobstructed (n = 52) or indeterminate (n = 20) based on the initial ^{99m}Tc-MAG3 scan.

Two other kidneys would have been classified as obstructed if OE had been combined with the standard parameters. In isolation, the OE correctly predicted 20 of 22 (91%) obstructed kidneys. The initial OE was normal in two kidneys subsequently shown to have obstruction. One of these occurred in a child with an unsuspected duplex kidney with obstruction in the lower pole moiety. Reanalysis using separate ROIs over the upper and lower pole yielded an abnormal OE in the lower pole. In the second patient, the original ROI underestimated the size of the renal pelvis.

In the group initially classified as unobstructed, 51 kidneys remained unobstructed at follow-up. Output efficiency was normal in these 51 kidneys. In the remaining kidney, OE was abnormal at 73%. Obstruction was subsequently diagnosed at surgery.

In the indeterminate group, two HN kidneys were subsequently shown at surgery to have PUJ obstruction. Output efficiency was abnormal in both of these. Eighteen HN kidneys were shown to be unobstructed at follow-up. Output efficiency correctly predicted this in 10 of 18 cases (56%).

A summary of the results comparing standard criteria with OE is shown in Table 1; OE performance in the indeterminate group is shown in Table 2; and the accuracy of OE is presented in Table 3.

Using exhaustive search multivariate logistic regression analysis, only OE ($p < 0.001$) and reduced uptake by visual assessment ($p = 0.058$) were independently associated with obstruction ($R^2 = 0.726$). Output efficiency was independently significant ($p < 0.001$) at a threshold of 71% ($R^2 = 0.58$). In this study, an OE threshold of 79% (2 s.d. below the mean) was used to discriminate between obstruction and no obstruction.

TABLE 2
OE Performance in the Indeterminate Group

Final outcome	No. of kidneys	Detection by OE
Obstruction	2	2/2
No obstruction	18	10/18

*n = 20 kidneys in the indeterminate group.

A subgroup with HN and reduced differential function (≤40%) was also studied (n = 20 kidneys). The differential function ranged from 25% to 40% (mean, 36% ± 5.3%). The skewed distribution in this subgroup limited the usefulness of the s.d. The degree of HN was reported only if the ultrasound images were available for review (11 patients). Severe HN was present in six patients (mean differential function, 32.5% ± 5.2%; range, 25%–40%), and mild/moderate HN was present in five patients. The initial OE was <79% (abnormal) in all 7 kidneys confirmed to be obstructed and >79% in 9 of 13 unobstructed kidneys. In these kidneys, OE had a sensitivity for obstruction of 100%, a specificity of 82% and an accuracy of 80%.

In the catheterized patients (n = 21 HN kidneys), the OE correctly stratified all kidneys as obstructed or unobstructed. In the remaining 70 HN kidneys, OE was abnormal in 8 kidneys shown to be unobstructed at follow-up and normal in 2 kidneys subsequently proven to be obstructed. The difference in accuracy between the two groups was not statistically significant ($p = 0.16$). In the noncatheterized group, the eight kidneys with abnormal OE and no obstruction had a diuretic $T\frac{1}{2}$ values of <10 min (one kidney), 10–20 min (five kidneys) and >20 min (two kidneys). These kidneys were classified by standard criteria, including the postvoid images, as unobstructed (three kidneys), indeterminate (three kidneys) and obstructed (two kidneys).

The 16 patients over 1 yr of age (20 HN kidneys) who received the lower furosemide dose of 0.5 mg/kg were all correctly classified as obstructed or unobstructed using OE.

DISCUSSION

The greater availability of prenatal ultrasound has increased the detection of fetal HN and the need for further evaluation in the postnatal period. Neonatal HN is a feature common to many conditions, including current or previous obstruction, vesicoureteric reflux, urinary sepsis, a noncompliant bladder and congenital malformations. Optimal postnatal management requires identification of patients with obstruction who will need surgery to preserve renal function.

Diverse opinions exist on the definition and diagnostic criteria for obstruction. Definitions range from ureteric resistance, which generates increased intrapelvic pressure (*8*), to a retrospective definition requiring renal functional loss (*9*). The need for functional deterioration may defeat the purpose of early diagnosis and has been likened to waiting for a tumor to metastasize before diagnosing cancer (*10*).

Similarly, the criteria for surgery vary from HN with reduced differential function of <35%–40% (*11,12*) to further decrease

in differential function of >10%, no matter what the baseline differential function and/or increasing HN on ultrasound (*13*). Early surgery has been recommended to allow the kidney "its full potential of functional recovery" (*14*). However, improved relative and total renal function without surgery in a cohort with unilateral HN and differential function of <40% has been reported (*13*). The dilemma is not whether obstruction requires surgery but in diagnosing obstruction.

The diagnostic difficulty, particularly in neonates, is attributed to multiple factors, including reduced renal function in early life, the maturational urinary tract changes and the volume and compliance of the HN system, which may all adversely affect the accuracy of diuretic renography (*15,16*). However, diuretic renography maintains an important role in most diagnostic algorithms. Several methods, including the extraction factor (*17*), the normalized clearance to uptake slope ratio (*18*), the renal growth–renal function chart (*19*) and the parameter we studied, OE (*5*), have been introduced with the aim of improving diagnostic accuracy.

The major findings of this report are: reduced OE and reduced uptake by visual assessment are independent significant predictors of obstruction, even in renal dysfunction; the lower limit of normal for OE is >89% (mean − 2 s.d.) for normal kidneys and >79% for unobstructed, HN kidneys; OE has a diagnostic accuracy of 89%; and the routine use of OE should help categorize pediatric patients more accurately.

Previous reports have demonstrated similar normal OE values of 79%–99% in adults (*5*) and of >85% in children (*6*) and an accuracy of 94% (*5*). Our two false-negative cases highlight a potential limitation if the ROI incorrectly estimates the size of the HN system. Our false-positive cases may be due to inherent limitations of this technique, technical faults or, possibly, spontaneous improvement, as has been reported by others (*13,16*).

The imaging diagnosis of obstruction in kidneys with marked HN and reduced function is fraught with difficulty because the diuretic response is dependent on the level of renal function; and clearance varies directly with the flow rate but inversely with the volume of the system (*15*).

In our subgroup with reduced differential function (mild reduction), OE had a sensitivity for obstruction of 100%, a specificity of 82% and an accuracy of 80%. This suggests that OE remains a useful parameter in the setting of mild dysfunction. The value of OE in severe dysfunction could not be assessed in this study.

There was a predominance of male infants (70%) in our study and in the cohort with proven obstruction (73%). Previous reviews of pediatric PUJ abnormalities have also observed a greater incidence in boys, particularly in those under 1 yr of age (*20,21*). Male sex, however, was not a statistically significant predictor of obstruction in our study.

Potential limitations of this study include the selective urinary catheterization and age-related furosemide dose.

Routine catheterization is recommended in the combined report from the Society of Fetal Urology and the Pediatric Nuclear Medicine Council (*22*). However, for practical reasons and to minimize patient distress related to an additional procedure, catheterization was only performed if vesicoureteric reflux or a suspected VUJ abnormality was present. In our study, the accuracy of OE was higher in the catheterized group; however, this did not reach statistical significance. Although maturational urinary tract changes may account for some of the "false" results in the noncatheterized group, routine catheterization may further improve the accuracy of OE.

A lower furosemide dose in patients over 1 yr of age (0.5 mg/kg) may potentially reduce the accuracy of diuretic renography because the furosemide effect is dose-dependent (*15*). However, at this age, renal function is generally better than in the neonatal period, and the pediatric dose of 0.5 mg/kg complies with manufacturer's recommendations (*23*). In our study, the patients receiving the lower dose were not disadvantaged and were all correctly classified as obstructed or unobstructed using OE.

CONCLUSION

OE is a useful additional parameter in the assessment of pediatric HN. In normal kidneys, OE should exceed 89%, and in unobstructed HN kidneys, it should exceed 79%. Decreased OE and reduced renal uptake qualitatively are the only independent, significant predictors of obstruction. Output efficiency remains useful in kidneys with mildly reduced function. In conjunction with standard parameters, OE may improve the diagnostic accuracy of diuretic renography.

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