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## EDITORIAL

# The Ongoing Challenge of Diagnosis and Treatment of Urinary Tract Infection, Vesicoureteral Reflux and Renal Damage in Children

In this issue of the *Journal*, Mozley et al. provide an opportunity to comment on several aspects sur-

rounding the diagnosis and treatment of vesicoureteral reflux (VUR) and urinary tract infection (UTI) as well as the identification of renal damage.

The goals of the physician taking care of children with urinary tract infection are to avoid renal damage if possible, or, if damage has already oc-

curred, to prevent it from progressing further (1-5). Renal scarring can lead to growth failure, hypertension and even chronic renal failure (6, 7). When the diagnosis of UTI in children is made (clinical history, general appearance of the child, urine analysis, urine culture, etc.), several questions

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should be addressed. One question is whether the febrile child (with or without signs of toxicity) has pyelonephritis. Other questions are whether the child has VUR, or hydronephrosis associated with the UTI. Answers to these questions are important for a proper assessment of the patient with UTI and should help the physician to arrive at the most appropriate diagnosis, decide on therapy, and plan the patient's follow-up. Differentiation of lower urinary tract infection from upper urinary tract infection based on clinical and laboratory findings is very difficult (8). Risk factors for the development of renal damage include the following: age of the patient, time to diagnosis, time from the initiation of therapy, bacterial virulence and host resistance and associated anatomic or functional abnormalities. The majority of renal cortical damage is thought to occur most frequently before age five. However, new scarring and progression of scarring can occur in older children as well (2,5,9). By the time renal scarring has occurred, no remedial or preventive measures can be taken, therefore a sensitive test which can show renal cortical damage is of great importance. Modern medical imaging procedures are helpful to elucidate these questions with a reasonably high level of confidence.

#### **Diagnosis and Grading of VUR**

The incidence of VUR in the pediatric population is not well known, although it has been suggested to be in the range of 1%–2% (10). Currently, diagnosis of vesicoureteral reflux (VUR) in children is made first and most frequently in patients with the diagnosis of UTI. However, not all patients with VUR have UTI.

Findings in asymptomatic siblings of children with VUR may be of interest in the discussion of VUR and renal damage. Asymptomatic siblings of children with VUR (index children) exhibit a very high incidence of vesicoureteric reflux (11,12). This is not to imply that the incidence of reflux in the general population is as high as familial reflux. However, this fact suggests that VUR may be present in chil-

dren without any clinical evidence of the disorder. Of further interest is the indication that a significant number of refluxing asymptomatic siblings of index children may have renal cortical damage, even though their history does not reveal a prior diagnosis of UTI (13). It is widely believed among pediatricians that urinary tract infection in children may be underdiagnosed. Since the main indication for cystography in children is urinary tract infection, it follows that VUR may also be underdiagnosed. Therefore, it appears that VUR, pyelonephritis and renal damage in children can occur in the absence of symptoms referable to the urinary tract.

Vesicoureteral reflux varies in degree from mild to severe. Its severity has been classified by the anatomic appearance on radiographic voiding cystourethrography (VCUG). Although previous experience suggests that the chances for spontaneous cessation of VUR are worse with high VCUG grades. Mozley et al. found no significant association between the grade of VUR on initial VCUG and outcome. VUR grading on radiographic VCUG is relatively subjective and operator and technique dependent. Relying on intermittent fluoroscopy, VCUG has relatively narrow windows of opportunity to observe reflux. Radionuclide cystography can detect VUR during the entire examination and can demonstrate intermittent reflux since recording is continuous during the entire procedure. There is no one-to-one correlation of the grading or appearance of VUR on VCUG and radionuclide cystography (RNC). Many investigators use RNC results as a definitive diagnosis. Radionuclide cystography, however, indicates if VUR is mild, moderate or severe (14). The accompanying paper found no relationship between VCUG grade of VUR and normalized reflux volumes on RNC and suggests that quantitation of volume variables may be of diagnostic and prognostic significance.

#### **Spontaneous Cessation of VUR**

It is generally believed that approximately two thirds of mild-to-moderate

VUR tends to disappear spontaneously with maturation (15). Periodic RNC is rapidly becoming the standard to determine evolution of VUR in patients followed medically on prophylactic antibiotics. Low-grade vesicoureteral reflux exhibits a degree of variability; this should be kept in mind in serial assessment of patients on prophylactic antibiotics before deciding to discontinue such treatment. Previous work has shown that the apparent severity of VUR varies from moment to moment, from examination to examination, and from day to day. Vesicoureteral reflux most frequently improves on sequential observations. We have evaluated ureters from 240 patients with RNC 480 on two separate occasions. The period between observations averaged 13 mo (three mo to 3.7 yr). None of the patients had prior surgery, neurogenic bladder or other anatomical abnormality. This study revealed that 85% of the ureters showed either no change (55%) or decrease (30%) in reflux severity. However 15% revealed an apparent worsening in reflux severity (9%), or reflux was detected only on the second RNC (6%) (16). Two-stage RNC has also shown the variable nature of VUR (16,17,18). Perhaps two consecutive normal cystographic studies are more reliable than a single normal study to ensure that VUR is present or has disappeared.

#### **Medical vs. Surgical Treatment**

The choice of surgery or no surgery as an outcome measure for the evaluation of the predictive value of quantitative radionuclide cystography on the accompanying paper may not be well received by many colleagues. The decision of a surgeon to treat a child with VUR medically or surgically is dependent on many factors, including the severity of reflux, the surgeon's training and philosophy, failure of medical treatment, non-compliance with antibiotic prophylaxis, as well as on socioeconomic factors. It follows that change from medical to surgical therapy does not signify in all instances that medical treatment has failed. In general, medical treatment is consid-

ered a failure if breakthrough infection occurs while the patient is on appropriate antibiotic coverage, or that reflux persists beyond the age that most are expected to show resolution. The exclusion of patients who had surgery within two yr of presentation bias the data, and the assumption that these patients had a more severe degree of reflux cannot be substantiated. It would be interesting to include these patients as well as the reflux severity of those patients who grew out of the disorder within two yr of presentation. Perhaps statistical analysis of the entire patient set would have yielded different results and interpretations. In the same paper, the use of intravenous urography is mentioned as the method to determine if the patient has renal damage (scarring). It has been repeatedly shown, however, that both intravenous urography and ultrasonography are grossly insensitive for the detection of renal damage. Therefore, the number of patients with renal damage or scarring on the accompanying paper are likely to have been significantly underestimated. Technetium-99m-dimercaptosuccinic acid (DMSA) scintigraphy has been repeatedly shown to be the most sensitive test available for the diagnosis of renal cortical damage in children suspected of pyelonephritis (8,19,20).

#### Pyelonephritis and VUR

It is important to note that although pyelonephritis is frequently associated with VUR, pyelonephritis can exist in the absence of VUR. Vesicoureteral reflux is very common in children and patients found to have VUR are usually placed on long-term antibiotic prophylaxis to prevent UTI and the consequent reflux of infected urine into the upper urinary tract. It has been estimated however, that approximately 35% of all children with symptomatic UTI have VUR (21,22). A recent study of 150 consecutive patients confirmed that VUR and renal scarring may not coexist on the same patients. Eighty-eight of 300 kidneys (29.3%) had one or more cortical defects on <sup>99m</sup>Tc-DMSA scintigraphy 61% of which did not have evidence of

VUR. In the same study 72/300 kidneys (24%) had VUR, 38 (53%) of which had no evidence of cortical defect(s) (23). Therefore, it does not seem appropriate to base outcome only on the presence or severity of vesicoureteral reflux.

#### Bladder Capacity in Children

Bladder capacity in children is employed to refer to the functional bladder volume estimated or measured during cystography. Detection of VUR on cystography is dependent on bladder volume. It is important to fill the child's bladder at or near the maximum predicted bladder capacity. Prediction of functional bladder capacity in children is difficult at best since bladder capacity is not a constant and varies in the same patient with patient's size, age, anxiety, bladder irritability, etc. There are previously reported methods to predict bladder volumes in children (24,25). Mozley, et al. assume the total bladder capacity in children by assuming that an average human with a body surface area of 1.73 m<sup>2</sup> would have a maximum bladder volume of 500 ml. Although this may be a correct assumption, we find no evidence that it is, or if and how this method correlates with previous methods of predicting functional bladder capacity in children (14,26,27).

#### Quantitative Radionuclide Cystography

Mozley, et al. employ a method of quantitative RNC to estimate refluxed volume and bladder volume during the study. The method is not described in detail, and the reader should be aware that quantitative radionuclide cystography is difficult to perform—it requires meticulous attention to detail—and is therefore not widely used. The paper does not mention how their methodology was validated. The authors estimated reflux volume and confirmed many previous observations that VUR at low bladder volumes is more severe than reflux at high bladder volumes, and that high reflux volume is more significant than low reflux volume (14,28). Mozley et al. found no relationship between age,

sex, or number of UTI during the entire follow-up period and calculated reflux volumes.

For the past decades, diagnosis, treatment and follow up of vesicoureteral reflux has been based on the results of radiographic cystourethrography. This technique provides good spatial resolution, detects anatomic bladder abnormalities and greatly assists in the evaluation of the male urethra. Radionuclide cystography is a more sensitive technique for the detection of VUR, delivering 50–100 lower radiation dose than VUCG (1–2 mrad to the ovaries). Quantitatively RNC is feasible and probably more accurate than qualitative cystography (VUCG or RNC), providing information on bladder and reflux volumes during the entire observation period and measuring residual bladder capacity and voiding flow rates. With the use of dual lumen intravesical catheters, simultaneous information on bladder pressure during the examination is possible (14). The widespread practical use of this quantitative approach, however, awaits further clinical investigation.

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