

## LONG-TERM OUTCOME OF VESICoureTERAL REFLUX ASSOCIATED CHRONIC RENAL FAILURE IN CHILDREN. DATA FROM THE ITALKID PROJECT

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### ABSTRACT

**Purpose:** The nephropathy associated with vesicoureteral reflux (VUR) is one of the leading causes of chronic renal failure (CRF) in children. We describe the clinical course of the disease based on information available in the Italkid Project database, and analyze the predictive value of baseline renal function, age at VUR diagnosis and urinary protein excretion in relation to the risk of progressive renal failure.

**Materials and Methods:** As of December 31, 2001 the registry included a total of 343 patients (261 males) with a diagnosis of primary VUR, which was the leading single cause of CRF, accounting for 25.4% of all patients with CRF.

**Results:** The estimated risk of end stage renal disease (ESRD) by age 20 years was 56%. The patients with a creatinine clearance (Ccr) of less than 40 ml per minute at baseline had an estimated 4-fold greater risk of ESRD developing in comparison with those whose Ccr was 40 to 75 ml per minute. No significant difference in probability of disease progression to ESRD was found between subjects diagnosed with VUR at age 6 months or less and those diagnosed later (older than 6 months). Furthermore, children with normal urinary protein excretion (a urinary protein [uPr]/urinary creatinine [uCr] ratio of less than 0.2 in 36 patients) and low grade proteinuria (uPr/uCr 0.2 to 0.8 in 34 patients) at baseline showed a significantly slower decrease in mean Ccr than those with moderate proteinuria (uPr/uCr greater than 0.8 in 34 patients). Hypertension and/or antihypertensive treatment (including antiprogessive drugs) were reported in 29.1% of patients.

**Conclusions:** The results of the present study define the long-term risk of ESRD in a large population of children with CRF and VUR, and provide some critical information for identifying the prognosis.

**KEY WORDS:** vesico-ureteral reflux; kidney failure, chronic; treatment outcome

The nephropathy associated with vesicoureteral reflux (VUR) is the leading cause of chronic renal failure (CRF) in children.<sup>1,2</sup> The natural history of the disease and long-term renal prognosis are poorly defined, thus making it difficult to predict renal outcome in any individual child with a diagnosis of CRF and VUR.

The widespread use of antibiotic prophylaxis against urinary tract infections and the surgical correction of VUR have led to the expectation that renal damage would be decreased,<sup>3–6</sup> and the development during the last 10 years of prenatal ultrasound screening to detect urological malformations has further increased the theoretical possibility of decreasing the risk of CRF by allowing early diagnosis and therapy. However, there is still little information<sup>6</sup> concerning the impact of these strategies on the prevention of end stage

renal disease (ESRD) in children with VUR whose renal function is already impaired.

This article describes the natural history of VUR associated CRF based on information available in the database of a nationwide registry of CRF in children (Italkid Project), and analyzes the impact of age at VUR diagnosis on the risk of progressive renal failure, and the predictive value of baseline renal function and urinary protein excretion in relation to renal outcome.

### PATIENTS AND METHODS

The Italian Pediatric Registry of Renal Failure (Italkid Project), which was started in 1990, contains records of children in Italy meeting the 2 inclusion criteria of 1) creatinine clearance (Ccr) less than 75 ml per minute per 1.73 m<sup>2</sup> body surface area according to Schwartz's formula<sup>7</sup> (for children younger than 1 year the registration forms include a table of age and gender specific limits for serum creatinine (as mean

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serum creatinine +3 SD) and 2) age younger than 20 years at registration. The clinical and biochemical data of the registered patients are updated every year until the beginning of renal replacement therapy or death. The general methodology of the ItalKid Project (organizational structure, reporting procedures and data quality control) has been described in detail elsewhere.<sup>1</sup>

As of December 31, 2001 the Registry included a total of 1,348 patients reported by 112 centers. This study is focused on the 343 patients with primary VUR associated CRF. Patients with VUR secondary to other urinary abnormalities (posterior urethral valves, urethral atresia, megalourethra, neurogenic bladder, complex uropathies) were excluded from study. This analysis is based on numerically different subpopulations depending on the data available for each child and the purpose of the individual analysis itself.

**Renal outcome and role of baseline Ccr.** The analysis involved 322 subjects (245 males) whose mean age  $\pm$  SD at registration was  $6.5 \pm 5.1$  years and whose mean Ccr was  $48.8 \pm 20.1$  ml per minute per  $1.73 \text{ m}^2$ . The 21 patients with incomplete information were excluded from study. Renal survival was calculated for the population as a whole and for the 2 subgroups with baseline Ccr less than 40 ml per minute (in 100 patients) and 40 to 75 ml per minute (in 222 patients).

**Progression and age at VUR diagnosis (in 187 patients, 144 males).** Between 1995 and 1997 a special survey of registered patients with a diagnosis of primary VUR associated CRF was performed to collect information regarding age at diagnosis of uropathy. The analysis excluded the patients whose age at VUR diagnosis was unknown.

**Progression and urinary protein excretion (in 104, 90 males).** The analysis of the predictive role of urinary protein excretion in relation to CRF progression excluded the patients with an age of 2 years, or less baseline Ccr 20 ml per minute or less per  $1.73 \text{ m}^2$ , treatment with angiotensin converting enzyme inhibitors, a followup of 1 year and unreported baseline urinary protein excretion levels. Proteinuria was analyzed using the urinary protein-to-creatinine ratio (uPr/uCr), with the patients divided into 3 groups on the basis of baseline urinary protein excretion values of normal uPr/uCr less than 0.2 (0.2 is the upper normal limit), low uPr/uCr 0.2 to 0.8 and moderately high uPr/uCr greater than 0.8. The cutoff point between the low grade and moderate proteinuria groups was identified as the median abnormal uPr/uCr level. The primary outcome measure was the rate of CRF progression, calculated as the yearly decrease in Ccr throughout followup, delta Ccr ( $\Delta\text{Ccr}$ ) in ml per minute per  $1.73 \text{ m}^2$  year. Arterial blood pressure (BP, given as mean blood pressure) was analyzed on the basis of the age and gender specific standard deviation score (SDS) using the 1987 reference values of the Task Force on Blood Pressure Control in Children.<sup>8</sup>

**Statistical analysis.** All of the results are expressed as mean values  $\pm$  SD except for the uPr/uCr ratio, which is given as median value and range because of the nonnormal distribution.  $\Delta\text{Ccr}$  was calculated as the difference in Ccr between baseline and end of followup divided by number of years of followup. The between-group differences at baseline were assessed by means of ANOVA. The contingency table was analyzed using the chi-square test. The survival analysis was based on the Kaplan-Meier method, and the between-group differences in survival rates in the life table analyses were evaluated using log rank statistics. The end point for the life table analyses was ESRD and  $p < 0.05$  was considered statistically significant.

## RESULTS

Between January 1, 1990 and December 31, 2001 a total of 1,348 pediatric patients with CRF were identified, 343 (25.4%) of whom had a diagnosis of primary VUR associated CRF. The female-to-male ratio was 1:3.2. Unilateral renal

agenesis was reported in 33 patients (9.8%) and polycystic kidney in 9 (2.6%). Figure 1 shows the frequency distribution of reflux grades by gender at diagnosis in the 323 renal units recorded (164 patients) in the database, and indicates that VUR is significantly more severe in males ( $p < 0.002$ ). As of December 31, 2001, 47 patients (13.7%) had ESRD. Information concerning BP and antihypertensive treatment at baseline was available for 268 patients. A total of 35 (13.1%) patients were being treated with an antihypertensive agent (21 with an angiotensin converting enzyme inhibitor) and 31 (11.5%) had a mean arterial pressure of more than the 95th percentile for age and gender, but only 12 (4.5%) had severe hypertension (MAP greater than 99th percentile).

**Renal outcome and role of baseline Ccr.** The estimated risk of ESRD developing by age 20 years was 56% in the population as a whole (fig. 2). The patients with a baseline Ccr of less than 40 ml per minute per  $1.73 \text{ m}^2$  had an estimated 4 times greater risk of ESRD developing in comparison with those whose Ccr was 40 to 75 ml per minute per  $1.73 \text{ m}^2$ . The decrease in kidney survival was not linear with age since there was a sharp decrease during puberty and early postpubescence.

**Progression and age at VUR diagnosis.** Figure 3 shows the cumulative percentage of patients with VUR by gender and

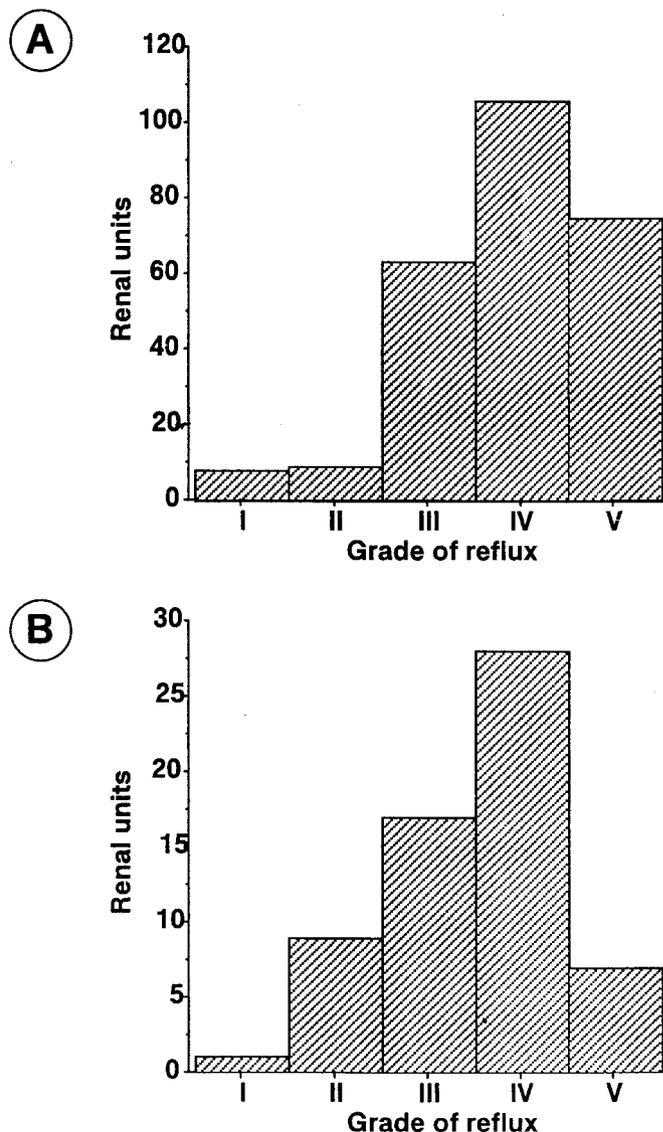


FIG. 1. Frequency distribution of reflux grades in 323 renal units of children with VUR associated CRF: 133 males (A) and 31 females (B). Reflux grade: males vs females ( $p < 0.02$ ).

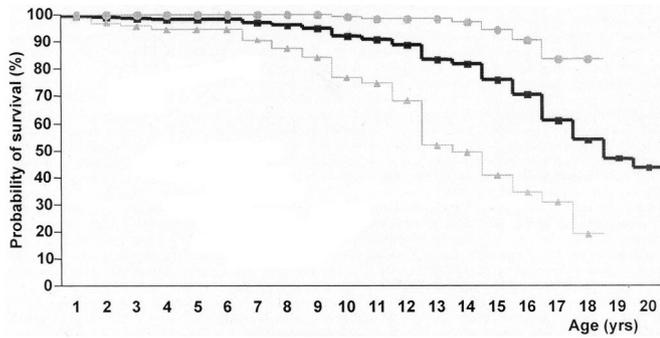


FIG. 2. Estimated kidney survival in patients with VUR associated CRF by age. Overall population (322 patients), —■—. Patients with baseline creatinine clearance less than 40 ml per minute (100 patients), —▲—. Patients with baseline Ccr 40 to 75 ml per minute (222 patients), —●—.

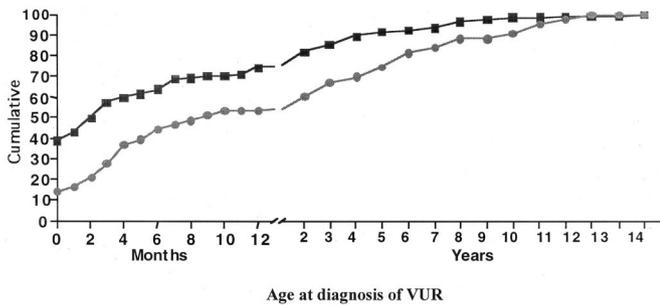


FIG. 3. Age at diagnosis of urinary tract malformations by gender in children with VUR associated CRF (187 patients). Males, —■—. Females, —●—.

age at diagnosis. The diagnosis was generally established early in life (at an overall median age of 3 months, range 0 to 180) but it was made significantly later in girls at age 9 months (range 0 to 156, 95% CI 21.2–49.3) vs 2 months (range 0 to 180, 95% CI 10.9–21.2). Analysis of renal survival by age at VUR diagnosis (fig. 4) did not reveal any significant difference in the probability of ESRD in the 76 subjects with an early diagnosis (age 6 months or less) and the 111 diagnosed later in life (older than 6 months, range 6.1 to 180). In 247 patients a detailed surgical history was available, with 176 (71%) having undergone ureteroneocystostomy by the time the survey on surgical correction of VUR was performed. Figure 5 shows the delay between age at VUR diagnosis and age at surgical intervention. The average delay was 11.3 ± 18.9 months and only 38 patients (21.6%) had surgical intervention postponed for more than 12 months.

**Progression and urinary protein excretion.** The relationship between the progression of renal failure (the decrease in Ccr

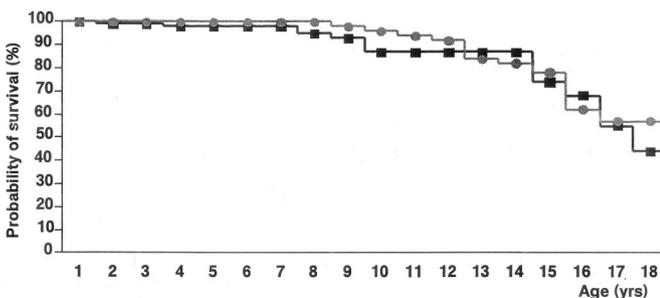


FIG. 4. Estimated kidney survival in children with VUR associated CRF by age at VUR diagnosis. Diagnosis of VUR at age 6 months or less (111 patients), —■—. Diagnosis of VUR at age older than 6 months (76 patients), —●—.

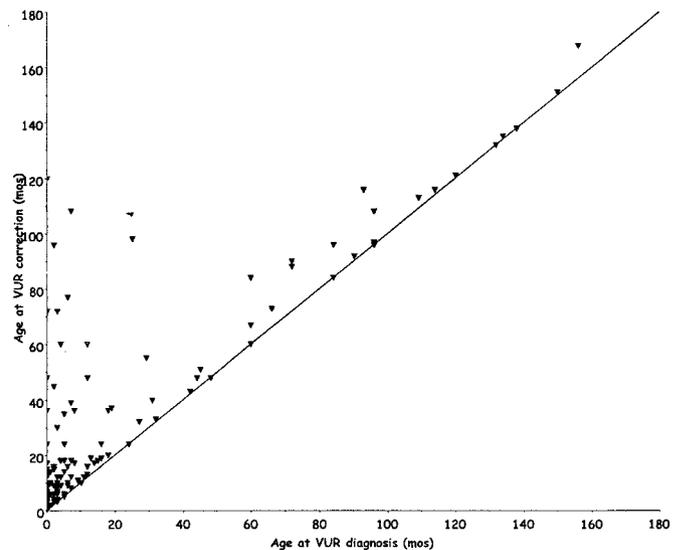


FIG. 5. Delay between age at VUR diagnosis and age at ureteroneocystostomy.

expressed in ml per year) and the rate of urinary protein excretion (expressed as the uPr/uCr ratio) could be analyzed in 104 children whose general characteristics are shown in the table. The median uPr/uCr ratio was 0.39 (range 0.01 to 7.21), and only 3.8% had severe proteinuria (uPr/uCr greater than 3.5). The table also shows the baseline clinical and laboratory parameters of these patients divided into 3 groups on the basis of baseline uPr/uCr values. Gender, age, followup and mean blood pressure SDS distributions were similar in the 3 groups, but baseline Ccr was significantly lower in the patients with moderate proteinuria.

The mean rate of Ccr decrease ( $\Delta$ Ccr) in the population as a whole was  $-0.68 \pm 4.05$  ml per minute per  $1.73 \text{ m}^2$  per year. As shown in figure 6 the patients with normal and low urinary protein excretion levels showed a nonsignificant loss of renal function (a mean  $\Delta$ Ccr of  $+0.59 \pm 2.28$  and  $-0.35 \pm 2.97$  ml per minute per  $1.73 \text{ m}^2$  per year, respectively), whereas the rate of functional decrease was significantly greater in those with moderate proteinuria ( $\Delta$ Ccr  $-2.36 \pm 5.67$  ml per minute per  $1.73 \text{ m}^2$  per year,  $p < 0.01$  vs the normal and low uPr/uCr groups). Analysis of renal damage progression in terms of kidney survival by baseline urinary protein excretion levels showed that only patients with moderate proteinuria had a significantly higher risk of ESRD ( $p < 0.01$ ) during the 5 years of followup (as high as 50% in the moderately high uPr/uCr group vs 0% in the remaining 2 groups).

DISCUSSION

The results of the present study offer to the clinician an overview of the natural course of VUR associated CRF in a large cohort of children, and provide evidence concerning the role of baseline Ccr and urinary protein excretion in predicting the risk of progression to ESRD. Our main findings are that children with VUR associated CRF have a generally poor renal prognosis. Almost 60% require renal replacement therapy before the age of 20 years, and this poor outcome becomes evident during and soon after puberty. However obvious as it may seem, it is worth pointing out that patients with a greater initial impairment in renal function are at greater risk for ESRD, which may help to define the long-term prognosis. Furthermore, once established the course of renal impairment does not seem to be influenced by age at VUR diagnosis. However, it is important to stress that since we analyzed patients whose renal function was already im-

## Baseline patient characteristics and segregation by baseline protein excretion levels

	Overall Population	Urinary Protein Excretion		
		Normal	Low	Moderate
No. pts	104	36	34	34
No. male/female	90/14	29/7	30/4	31/3
Mean yrs followup $\pm$ SD	3.6 $\pm$ 1.1	3.6 $\pm$ 1.0	3.4 $\pm$ 1.2	3.6 $\pm$ 1.0
Mean age $\pm$ SD (yrs)	7.6 $\pm$ 4.3	7.1 $\pm$ 3.9	8.5 $\pm$ 4.6	7.2 $\pm$ 4.5
Mean BP $\pm$ SDS	0.26 $\pm$ 1.1	0.34 $\pm$ 1.0	0.42 $\pm$ 1.4	0.01 $\pm$ 0.9
Mean Ccr ml/min/1.73 m <sup>2</sup> $\pm$ SD	55.8 $\pm$ 15.5	63.5 $\pm$ 11.3	57.2 $\pm$ 13.4	46.1 $\pm$ 16.6*
Median uPr/uCr (range)	0.39 (0.01–7.21)	0.01 (0.01–0.19)	0.42 (0.21–0.75)	1.62 (0.95–7.2)

\* Moderate vs normal and low  $p < 0.0001$ .

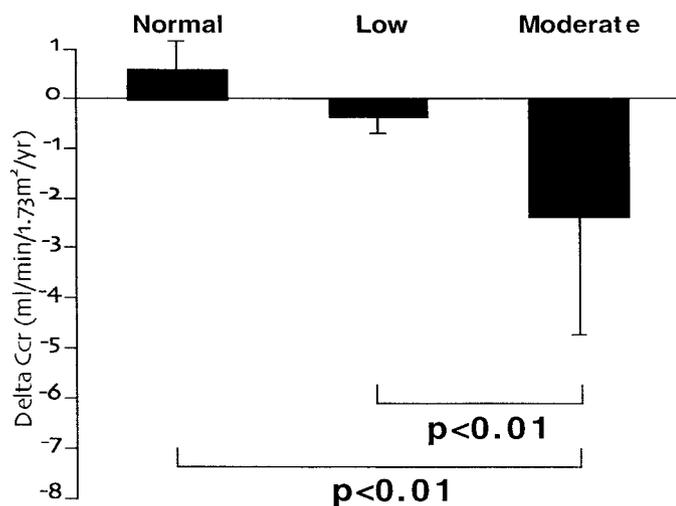


FIG. 6. Mean (and SE) rate of decrease in creatinine clearance (Delta Ccr) by baseline urinary protein excretion.

paired at study entry, this conclusion is limited to the course of the disease after the development of renal insufficiency, and obviously does not consider the impact of early diagnosis of VUR on the risk of the development of renal insufficiency itself.

However, most of the children were diagnosed early in life (during the year 1 or before birth) and it can be speculated that they had too little time to be exposed to multiple episodes of pyelonephritis. However, infections are not systematically recorded in the Italkid database, and this clearly represents a limitation. Perhaps we are mainly evaluating a population of children with congenital renal damage (with various degrees of associated hypodysplasia) who cannot benefit from any specific therapeutic maneuver other than the usual care of CRF.

Based on the observation that when the survey was performed 71% of the population had been already subject to surgical intervention of VUR (mainly within the 12 months subsequent to VUR diagnosis), it can be stated that surgery still remains the preferred management modality of VUR in Italy. Unfortunately a comparison of the nephropathy progression between subjects who underwent surgery early after VUR diagnosis and those who received more conservative management is not yet possible due to age and followup related systematic biases in the 2 groups. Patients who were not subject to surgical intervention are much younger and have a shorter followup which prevents us from drawing reliable conclusions on the risk of long-term outcome.

It has been increasingly recognized during the last 10 years that urinary protein excretion is a reliable predictor and possible cause of poor outcomes in diabetic and nondiabetic adults with proteinuric renal diseases.<sup>9–13</sup> However, little is known about its role in pediatric renal diseases,<sup>14</sup> particularly in patients with VUR associated CRF who, unlike adult patients with nephropathy (who mainly suffer

from glomerular diseases) do not have severe proteinuria. Our finding that proteinuria is also a strong predictor of disease progression in such cases are based on 2 different indicators of yearly decrease in Ccr and kidney survival. Proteinuria was measured as the urinary protein-to-creatinine ratio, which has been shown to be at least as reliable as 24-hour urinary protein excretion in adults.<sup>15,16</sup> The use of this ratio seems to be particularly appropriate in our study because 24-hour urine collections would have 2 possible sources of inaccuracy, the objective difficulty of obtaining precise urine collections from children and the incompleteness of urine output in patients with associated VUR.

The patients with moderate urinary protein excretion at the beginning of the observation period showed a much faster Ccr decrease than those with a low or normal uPr/uCr ratio. Furthermore, after 5 years of followup, kidney survival was 100% in patients with normal and low urinary protein excretion but only 50% in those with moderate proteinuria. It is worth pointing out that, even when abnormal, proteinuria was never severe in our population. The median uPr/uCr ratio of patients with moderate proteinuria was 1.62, which is far from nephrotic levels (greater than 3.5).<sup>15</sup>

Although our data show that baseline protein excretion is a strong predictor of renal disease progression, they are unsuitable for establishing a cause and effect relationship. However, experimental<sup>17,18</sup> and clinical<sup>19</sup> observations support the existence of such a relationship on the basis of the theoretical framework that the increased glomerular filtration of proteins induces tubular reabsorption and accumulation in the cytoplasm of proximal tubular cells. The toxic effect of this protein overload is to break the basement membrane and release the cell content into the interstitium, thus triggering an inflammatory reaction, and consequent progressive tubulointerstitial and glomerular damage. Another interesting finding in our study population is the relatively low prevalence of hypertension, although renal parenchymal dysplasia and renal scars are reported as frequently associated with high blood pressure in children.<sup>20</sup>

Finally, we want to point out that the present analysis, although based on a remarkable number of patients which enhances study power, lacks sensitivity with regard to several events characterizing the clinical history of any single patient with VUR. These events cannot be recorded by a registry study and, although minor, they might be relevant to the outcome of nephropathy. With this limitation in mind the results of this study define the long-term risk of ESRD in a large population of children with VUR associated CRF, and demonstrate that a baseline Ccr of less than 40 ml per minute and moderate proteinuria are strong predictors of a poor outcome. Therefore, the results offer some insights into the pathophysiology of the progressive loss of renal function and provide critical information for anticipating the so far unpredictable long-term prognosis.

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## EDITORIAL COMMENT

Urologists will find this article interesting and provocative. These data are derived from a recently published larger cohort of children with CRF (reference 1 in text) and demonstrates definitively that 25% of all children with chronic renal failure have vesicoureteral reflux as their underlying diagnosis. The demographics of the study group are most fascinating in that the vast majority present at a young age (median 3 months). This study supports my long held "Calvinistic Theory of Pediatric Urology," ie that ultimate renal outcome is quite likely predetermined (by fetal events) and that ESRD is not preventable regardless of surgical or medical management. It is regrettable that the current work does not tabulate the clinical course of the patients in terms of urinary tract infection but clearly the surgical interventions for reflux did not change the ultimate renal outcome. A corollary to this "doctrine" of renal predestination is that current management protocols of surgery and antibiotic prophylaxis in children with normal renal function do little to curb the development of renal failure, since this population is not at risk. Recent publications<sup>1</sup> (and reference 6 in paper) support this nihilistic view of reflux management. New scars may occur, but ESRD is not an outcome for the usual patients with vesicoureteral

reflux, urinary tract infection and initially normal renal function. This article demonstrates the clinical value of the uPr/uCr ratio, although I am uncertain why the test was applied only to children at least 2 years old. In any event this easily obtained assessment should find widespread use.

For the distribution of severity of VUR between boys and girls, the authors seem to have conducted the chi-square test using a contingency table, and  $p < 0.002$  was reported (however, 0.02 was mentioned in the figure legends). There are 2 problems with this approach. First, the data were quite sparse and a large sample chi-square test could be misleading. Also, the numbers of the contingency table were renal units and the majority of the cases included were bilateral. As a result the renal units in the analysis could be highly dependent, violating the independent assumption of the chi-square test.

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