

# Controlled Outcomes for Achievement of Urinary Continence among Boys Treated for Posterior Urethral Valves



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**Purpose:** We evaluated the age at which boys with a history of posterior urethral valves after no or minimal anticholinergic medication achieve urinary continence and the factors contributing to continence.

**Materials and Methods:** We reviewed the hospital records of all males treated for posterior urethral valves at a single institution between 1990 and 2008. Continence was considered to have been attained if no weekly wetting episodes occurred. We evaluated the influence of patient characteristics, including reduced kidney function and primary ring type ureteral stoma, on age at which continence was achieved.

**Results:** A total of 76 patients were assessed. Achievement of daytime and nighttime urinary continence was markedly delayed in patients (mean  $\pm$  SD age  $5.5 \pm 3.3$  years and  $5.4 \pm 3.0$  years, respectively) compared to the reference population ( $2.3 \pm 0.5$  and  $2.9 \pm 1.2$ ,  $p < 0.001$ ). Increased serum creatinine levels at age 5 years were associated with later daytime and nighttime continence (mean  $\pm$  SD  $6.0 \pm 3.2$  and  $5.5 \pm 2.6$  years, respectively, vs  $4.1 \pm 2.3$  and  $3.7 \pm 1.4$  years, respectively, in patients with normal serum creatinine,  $p \leq 0.05$ ). Prenatal or neonatal diagnosis of posterior urethral valves was associated with significantly delayed achievement of daytime continence compared to cases diagnosed later (mean  $\pm$  SD  $5.9 \pm 3.6$  vs  $4.1 \pm 1.8$  years,  $p = 0.02$ ). Patients with high nadir serum creatinine and vesicoureteral reflux initially also were at increased risk for urinary tract infections ( $p = 0.003$  and  $p < 0.001$ , respectively).

**Conclusions:** Patients with posterior urethral valves achieve daytime and nighttime urinary continence significantly later than their healthy peers. Prenatal or neonatal diagnosis and high serum creatinine are associated with later attainment of continence.

## Abbreviations and Acronyms

PUV = posterior urethral valve

UTI = urinary tract infection

VUR = vesicoureteral reflux

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POSTERIOR urethral valves are the most common cause of lower urinary tract obstruction in boys, being accompanied by variable dysfunction of the lower urinary tract.<sup>1</sup> Valve ablation usually resolves the obstruction. However, dysfunction of the bladder may follow the patient throughout life.<sup>2,3</sup> Typically patients

suffer from detrusor overactivity and a low compliance bladder in early childhood, and later the bladder may become underactive and distended.<sup>4-6</sup> The classic daytime voiding pattern in early childhood of passing small volumes at frequent intervals may affect the success of toilet training.<sup>5,7</sup> Additionally the impaired concentrating

ability of the kidneys that is present in many cases may lead to polyuria, contributing to incontinence and persistence of hydronephrosis.<sup>8,9</sup> At an older age poor emptying of the bladder may also lead to persisting incontinence.<sup>10</sup>

The age at which children are weaned from diapers for urine varies widely between reports, and there is a lack of controlled series on the achievement of dryness among these patients.<sup>11–14</sup> We determined the age at which children with a history of PUVs who have received no or minimal anticholinergic medication achieve daytime and nighttime urinary continence in relation to healthy controls in the general population, and evaluated the factors influencing this finding.

## MATERIALS AND METHODS

We retrospectively reviewed the records of all patients treated for PUVs between 1990 and 2008 at the Children's Hospital, University of Helsinki. Following institutional ethical board approval a total of 76 patients were identified. No patient was excluded or lost to followup. Diagnosis of PUV was based on voiding cystourethrogram and confirmed by urethral endoscopy. Age at presentation with PUV, presence of VUR at diagnosis, occurrence of UTIs after valve ablation, and age at attainment of daytime and nighttime urinary continence were documented. Febrile and afebrile symptomatic UTIs for which patients received antibiotic treatment were included in the analysis.

Median age at diagnosis of PUVs was 0.02 years (range 0 days to 9.8 years). Standard transurethral ablation of the valves by hot loop or cold knife resectoscope had been performed by a consultant pediatric surgeon in all cases. A temporary ring type ureterocutaneostomy allowing bladder cycling was used in 18 neonates (24%) and vesicostomy in 1 (1%). Diversions were closed after 1 year. Modes of presentation of PUVs are outlined in table 1.

The greatest serum creatinine value at presentation and nadir value during the first year after valve ablation and at age of 5 years were registered. Our institutional reference values for serum creatinine by age are 37 to 98  $\mu\text{mol/l}$  at 0 to 2 days, 15 to 72  $\mu\text{mol/l}$  at 3 to 7 days, 10 to 56  $\mu\text{mol/l}$  at 8 days to 2 years and 10 to 48  $\mu\text{mol/l}$  at 5 years. We analyzed the effects of renal function (primary and later), age and presence of VUR at diagnosis of PUV, and temporary diversion on age at which the patient became dry. Continence was considered to have been attained if

no weekly wetting episodes occurred, criteria that we have found reliable and relevant in clinical practice. The development of continence in PUV cases was compared to the normal unselected child population. Urodynamic findings were not included in our analysis because we have observed that they rarely influence our clinical decision making.

## Controls

Recently our research group collected a population of 594 subjects 4 to 26 years old who had been randomly selected from the Population Register Centre of Finland.<sup>15</sup> Controls consisted of age and gender matched boys from this population.

## Patients with PUVs Born between 1973 and 1989

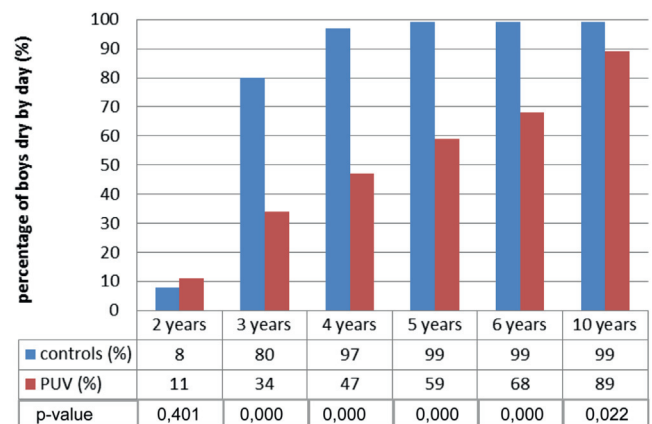
We collected data of all patients with PUVs born between 1973 and 1989 and treated at the Children's Hospital, University of Helsinki, and compared whether development of continence had changed through time. During recent decades families of patients with PUV at our institution have received systematic guidance on the early institution of toilet training in the form of frequent and double voiding.

## Statistics

The Student t-test was used to compare the groups for a possible difference in dryness age and to evaluate the role of VUR. The Fisher exact test was used to compare the proportion of continent patients in different age groups. Cross-tabulation and Pearson chi-square tests were used to compare the age of attaining continence, and for comparison of groups with and without VUR and UTIs. SPSS®, version 19.0 was used for statistical analysis. P values were 2-sided and  $p < 0.05$  was considered statistically significant.

## RESULTS

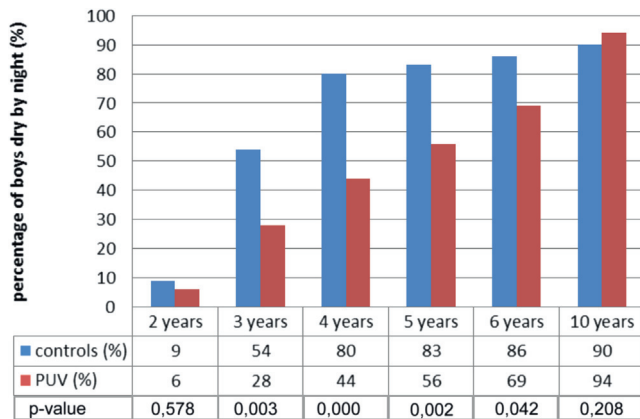
In relation to the control reference population patients with PUVs achieved daytime and nighttime continence significantly later (figs. 1 and 2), at



**Figure 1.** Comparison of daytime incontinence between patients with PUVs and controls.

**Table 1.** Diagnosis of PUVs

Presentation	No. (%)
Prenatal	30 (39)
Neonatal	20 (26)
Infection	22 (28)
Other	4 (5)
<b>Total</b>	<b>76 (100)</b>



**Figure 2.** Comparison of nocturnal enuresis between patients with PUVs and controls.

a mean  $\pm$  SD age of  $5.5 \pm 3.3$  and  $5.4 \pm 3.0$  years, respectively, compared to  $2.3 \pm 0.5$  and  $2.9 \pm 1.2$  years among controls ( $p < 0.001$ ). As outlined in table 2, patients diagnosed prenatally or neonatally attained daytime urinary continence significantly later than those who were older at diagnosis ( $5.9$  vs  $4.1$  years,  $p = 0.02$ ). Similarly patients with reduced renal function tended to become continent at an older age. Nadir serum creatinine values after diagnosis did not relate as strongly to the development of continence as did the serum creatinine values at age 5 years. As nadir creatinine values did not significantly relate to continence outcomes,

**Table 2.** Factors affecting achievement of daytime and nighttime urinary continence in patients with PUVs

	Achievement of Daytime Continence			Achievement of Nighttime Continence		
	No. Pts	Mean $\pm$ SD Age (yrs)	p Value	No. Pts	Mean $\pm$ SD Age (yrs)	p Value
Nadir creatinine ( $\mu\text{mol/l}$ ):			0.31			0.07
Less than 70	36	$5.3 \pm 3.3$		36	$4.9 \pm 3.1$	
Greater than 70	10	$6.5 \pm 3.2$		9	$7.0 \pm 2.9$	
Creatinine ( $\mu\text{mol/l}$ ) at 5 yrs:			0.05			0.03
Less than 50	26	$4.1 \pm 2.3$		25	$3.7 \pm 1.4$	
Greater than 50	16	$6.0 \pm 3.2$		14	$5.5 \pm 2.6$	
Age (mos) at diagnosis:			0.02			0.86
Less than 1	35	$5.9 \pm 3.6$		34	$5.3 \pm 2.7$	
Greater than 1	15	$4.1 \pm 1.8$		17	$5.1 \pm 3.7$	
VUR:			0.16			0.23
None	20	$4.6 \pm 2.9$		22	$4.7 \pm 2.1$	
Primary	30	$5.9 \pm 3.4$		29	$5.6 \pm 3.5$	
Stoma:			0.4			0.19
No	36	$5.1 \pm 3.2$		37	$4.9 \pm 3.0$	
Yes	14	$6.0 \pm 3.4$		14	$6.1 \pm 3.0$	
UTI after valve ablation:			0.88			0.08
No	20	$5.2 \pm 3.2$		24	$5.9 \pm 3.7$	
Yes	28	$5.4 \pm 3.3$		27	$4.4 \pm 1.9$	

further multivariate analyses of these variables were not performed.

Children with VUR (46 patients, 61%) tended to achieve daytime and nighttime urinary continence later than those without VUR (table 2), and patients with bilateral VUR achieved continence even later (mean  $\pm$  SD age at daytime continence  $6.9 \pm 2.5$  vs  $4.6 \pm 2.9$  years,  $p = 0.07$ , and at nighttime continence  $6.4 \pm 2.3$  vs  $4.7 \pm 2.1$  years,  $p = 0.16$ ). Patients with VUR initially had significantly higher creatinine levels at age 5 to 7 years (mean  $43$  vs  $108 \mu\text{mol/l}$ ,  $p = 0.01$ ). A total of 36 patients (47%) suffered from UTIs after valve ablation. UTIs were significantly more common in patients with (29 of 41, 71%) vs without (7 of 27, 26%) VUR ( $p < 0.001$ ). Patients with UTIs had higher primary creatinine values than those who did not have infections (mean  $\pm$  SD  $169 \pm 130$  vs  $91 \pm 61 \mu\text{mol/l}$ ,  $p = 0.003$ ). Creatinine values also remained higher later in childhood, although the difference was no longer statistically significant (mean  $\pm$  SD  $88 \pm 108$  vs  $53 \pm 28 \mu\text{mol/l}$ ,  $p = 0.12$ ). However, patients with infections did not attain continence significantly later than patients without UTIs ( $p \geq 0.08$ , table 2).

Although patients with a temporary ring type supraventricular diversion became toilet trained later than those without diversion, the difference was not statistically significant (table 2). Diverted patients had significantly higher mean  $\pm$  SD nadir creatinine values ( $175 \pm 80 \mu\text{mol/l}$ ) than nondiverted patients ( $41 \pm 29 \mu\text{mol/l}$ ,  $p = 0.01$ ). There was no significant difference in outcomes if the 19 patients with temporary urinary tract diversion were excluded. Six patients received oxybutynin for overactive bladder.

A total of 26 patients born before 1990 became daytime (mean  $\pm$  SD  $7.4 \pm 3.7$  years) and nighttime ( $7.2 \pm 3.6$  years) continent significantly later than the patients born after 1990 ( $5.5 \pm 3.3$  and  $5.4 \pm 3.0$  years, respectively,  $p = 0.03$ ). As with the patients born after 1990 (table 2), those born before 1990 with normal renal function (nadir serum creatinine values within normal limits) tended to become continent earlier than their counterparts with poor renal function (mean  $\pm$  SD age at daytime continence  $6.6 \pm 2.6$  vs  $9.0 \pm 3.7$  years,  $p = 0.38$ , and at nighttime continence  $6.4 \pm 2.8$  vs  $7.2 \pm 2.8$  years,  $p = 0.77$ ).

## DISCUSSION

In our study the patients with PUV achieved urinary continence significantly later than their peers from the general population. It has been established that even in healthy children wetting can lead to social distress, psychological problems and decreased quality of life.<sup>16,17</sup> In our previous study

quality of life was decreased in adults with urinary incontinence who had been treated for PUV in childhood.<sup>18</sup> Although incontinence is a common finding in patients with PUV, wide variations in actual age at continence attainment have been reported, and controlled studies are lacking. Parkhouse et al reported 55% daytime continence by age 5 years, while all patients were continent by 16 years.<sup>14</sup> In a study by Smith et al only 19% of patients had attained diurnal continence at age 5 years, and 46% at 10 years.<sup>19</sup> Of a group of infant valve patients followed to age 5 years 21% were continent at that age.<sup>11</sup> By comparison, Sarhan et al reported that 32 of their patients (49%) were continent at a mean age of 3 years.<sup>20</sup>

In a previous report from our institution 36% of 193 patients were still incontinent at age 6 years,<sup>21</sup> although daytime and nighttime continence were not separately analyzed as in the current series. Furthermore, in this study we compared the development of continence in patients born in different decades. During the last decades we have systematically guided families to early and scheduled toilet training and to double voiding during yearly or more frequent followup visits. We also perform urinary flowmetry and residual measurements by real-time ultrasound routinely during control visits to detect any bladder emptying issues. The guidance is likely to have been beneficial, since patients born after 1990 have become continent significantly earlier than those treated before this period. However, the possibility of selection bias affecting the results of our earlier series is acknowledged, as most of these patients did not undergo prenatal ultrasound investigations. Because of this issue, the diagnosis of PUV may have been delayed in some cases and affected the prevalence of subsequent bladder problems.

Daytime urinary incontinence at age 5 years has been identified as a risk factor for subsequent renal failure.<sup>12,14</sup> In agreement with this finding patients with poor kidney function in our series tended to become continent later than those with normal serum creatinine levels. An inverse correlation between filling detrusor pressures and glomerular filtration rate has previously been noted.<sup>14</sup> Chronically increased infravesical pressure that is reflected into the upper urinary tract may injure renal collecting tubules, resulting in antidiuretic hormone insensitivity and acquired nephrogenic diabetes insipidus.<sup>8,14,22</sup> The low glomerular filtration rates in PUV have been shown to correlate with high urine volumes and low urine osmolality.<sup>8,14</sup> Because of polyuria and decreased compliance, the bladder cannot store all of the urine throughout the night. The combination of a noncompliant thick walled bladder,

nephrogenic diabetes insipidus and incontinence with persistent upper urinary tract dilatation following valve ablation has been referred to as "valve bladder syndrome."<sup>9,10</sup> In our study high creatinine values as a marker of poor kidney function were related to delayed achievement of nighttime continence, and also to a tendency toward later daytime continence.

In our series patients diagnosed prenatally or neonatally achieved continence at an older age than those diagnosed later in infancy. While Podesta et al did not report the exact ages at which children became toilet trained, only 21% of their patients treated before age 21 months were continent by 5 years.<sup>11</sup> Those findings and ours support the notion that patients diagnosed earlier have a more severe form of PUV as reflected in the increased creatinine levels, and may have polyuria and more severe bladder dysfunction and thus later attainment of continence. However, contrasting findings have also been reported. In 2 series abnormal lower urinary tract function or delayed continence was more common in patients with a late diagnosis.<sup>12,13</sup> Regardless, in both series patients with a prenatal or neonatal diagnosis were comparatively rare. By comparison, 66% of the patients in our series (mostly consisting of those with the poorest renal function) were diagnosed prenatally or neonatally, and the overall median age at diagnosis was just 6 days. Differences in prenatal screening practices may have led to differences in survival patterns among patients with PUV, with downstream influences on the functional outcomes observed in retrospective series.

Otukesh et al found that the presence of VUR (in PUV cases) was a significant risk factor for the future occurrence of lower urinary tract dysfunction,<sup>12</sup> and a similar trend was observed in our series. Since impaired renal function is more common in patients with VUR,<sup>23</sup> the accompanying polyuria could impact bladder function. However, although VUR is a common finding in children with enuresis who have daytime incontinence, the influence of VUR itself on bladder function has remained unclear.<sup>24</sup>

In agreement with the notion that UTIs are common among patients with PUVs,<sup>25</sup> more than half of our patients experienced UTIs after the valve operation. It is well established that recurrent UTIs are a risk factor for renal scarring and, coupled with a high primary creatinine, are associated with an increased risk of renal failure.<sup>21,25</sup> Accordingly the patients with UTIs in our cohort had significantly greater primary creatinine values than those without infections, indicating that several risk factors for renal failure may have accumulated in the former group.

Early valve ablation has been reported to lead to better bladder compliance and function than supravescical diversion.<sup>13,26</sup> Jayanthi<sup>27</sup> and Close<sup>28</sup> et al noted that patients with urinary diversion were more likely to need bladder augmentation in the future. A requirement for primary bladder diversion has been associated with later age at toilet training,<sup>28</sup> although these patients also are often the most severely ill.<sup>29,30</sup> In our study ring type supravescical diversion to allow bladder cycling was performed only for patients with especially poor kidney function, and they had a nonsignificant trend for later toilet training age than patients without stoma. However, this observation more likely relates to poorer renal function in the stoma group than to the stoma itself.

The retrospective nature of our study means that the information concerning continence and serum creatinine relies on the frequency of control visits, which were not as regular or systematic before 1990 as they are today. This factor introduces the possibility of selection bias to the earlier data. During recent decades nearly all patients have been followed on a yearly basis, allowing for more complete data from the entire patient population. We also did not assess urine production, specific gravity or serum nadir creatinine in relation to achieving continence in our series. A limitation but also a strength of our study was that few of our patients had received anticholinergic medication, and those

who did were older than 5 years. Furthermore, no patient received alpha blockers. Therefore, our study demonstrates the outcomes that were achieved based on active urotherapeutic intervention alone.

Data on stooling history were not available for our series but would have been interesting to include. Additionally our definition of UTIs has included febrile and afebrile symptomatic but treated episodes, which should be considered when comparing other series. Overall although our findings suggest that achievement of urinary continence in patients with PUVs is significantly delayed compared to the control reference population, by age 10 years and after active urotherapeutic counseling there is no significant difference compared to peers in terms of continence. It would be interesting in future studies to evaluate whether routine use of anticholinergics could further improve achievement of dryness.

## CONCLUSIONS

Our findings suggest that achievement of urinary continence in patients with a history of PUVs who have not received anticholinergic medication is significantly delayed compared to the control reference population. Delayed continence and recurrent UTIs are especially common in patients with an early diagnosis and high serum creatinine levels.

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