POSTERIOR URETHRAL VALVES
EARLY FEATURES AND RENAL OUTCOME

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ACADEMIC DISSERTATION
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To my family
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ABSTRACT

Background. Posterior urethral valves (PUV) constitute the most common infravesical urinary obstruction in boys. PUV are often accompanied by severe consequences to the lower and upper urinary tract (LUT, UUT). They also represent a major urological cause for paediatric renal transplantations. Surgical options for primary management invariably aim at abolition of valves. However, temporary urinary diversion may sometimes be a viable alternative, especially in critically ill patients or preterm infants. Since no previous systemically analysed true long-term studies exist, early findings, treatment and their relations to late renal function are not clarified in many respects.

Aims. The clinical characteristics and renal outcomes of PUV were assessed. Also evaluated were the risk factors for the progression to end-stage renal disease (ESRD).

Patients and methods. All patients treated for PUV at Children’s Hospital, University of Helsinki, from 1953 to 2003 were identified from the hospital database. Age and mode of presentation, structural abnormalities, treatment, follow-up data and outcome were registered. In addition, the Finnish Kidney Transplantation Registry and the Finnish Population Register were reviewed to identify those who had progression to dialysis or renal transplantation or had demised.

Results. The diagnosis of PUV was made in 200 patients. Of all patients, 28 (14%) had a prenatal diagnosis. Cryptorchidism was found in 31 patients (16%) and inguinal hernia in 21 patients (11%). These two disorders were associated with more severe forms of PUV.

Urinoma was detected in 17 patients (9%). After onset of routine ultrasound (US) studies, the incidence was 15%. Of the 17 patients, 9 had perirenal urinoma, 6 urinary ascites and 2 urinothorax. At presentation and during follow-up, median creatinine values did not differ significantly between patients with and without urinoma or between cases with perirenal urinoma and those with urine ascites.

In the group of 25 infant PUV patients, cystometric bladder capacity (CBC) was a median of 22 ml (range 5 to 125) and maximal detrusor pressure during voiding (Pmax det) 112 cm H₂O (range 40 to 331). However, according to previous reports maximal voiding pressures were similar in an institutional control group and in male infant groups with different aetiologies. In our study, no correlation between high voiding pressures and poor primary kidney function was observed.
A significant increase in CBC and a decrease in Pmax det were registered at the one-year follow-up.

Vesicoureteral reflex (VUR) was observed in 127 PUV patients (64%). Bilateral VUR was present in 73 (37%) and unilateral VUR in 54 (27%). At presentation, refluxing patients had significantly higher serum creatinine values than patients without VUR. This was a distinctive feature in bilateral VUR and persisted at the 6- and 12-month follow-up visits. Reflux resolved spontaneously at a median of 1.28 years (range 0.04 to 15.16) after the release of the valvular obstruction.

Of all patients, 44 (22.8%) had progression to ESRD at the evaluation, which occurred at a median age of 31 years (range 6 to 69); 30 (68%) had developed renal failure as a child, before the age of 17 years, and 14 (32%) as adults. In this study, the highest age at the onset of ESRD was 34 years. According to Kaplan-Meier analysis, the life-time risk of ESRD was 28.5% (SE 3.8%). Patients with higher creatinine values during the first postoperative year had progression to ESRD at an earlier age. Early age, poor renal function, pneumothorax and bilateral VUR at presentation and postoperative recurrent urinary tract infections (UTIs) were risk factors for ESRD.

**Conclusions.** The incidence of cryptorchidism is 16-fold higher and the incidence of inguinal hernia 7-fold higher in PUV patients than in the normal population. Cryptorchidism and inguinal hernias are more common in patients with more severe PUV. The underlying pathophysiological mechanisms remain unclear.

The incidence of urinomas in PUV patients is currently 15%. Renal function is similar in PUV patients with and without urinoma. The abolition of valves is probably a sufficient operative procedure in most asymptomatic cases.

High voiding pressures were seen in infants around the ablation of the valves. No correlation between high voiding pressures and poor primary kidney function was observed. The voiding pressures were registered to decrease during the months following the release of the valvular obstruction.

The incidence of VUR at the time of presentation was high, 64%. Bilateral VUR was often accompanied by reduced overall kidney function. Kidneys with refluxing units had worse primary function than contralateral kidneys. Spontaneous resolution of VUR occurred in half of the ureters within 2 years of abolition of valves, more rapidly in unilateral than in bilateral cases. Antireflux surgery is most often not indicated.

Posterior urethral valves often lead to ESRD. After patients reached the mid-thirties, the risk subsided in this study. Early presentation, poor primary renal function, pneumothorax perinatally as well as VUR bilaterally and recurrent postoperative UTIs carry a risk for renal function deterioration and ESRD. These risk factors should be recognized and proper management initiated, with follow-up extending through childhood to adulthood.
This thesis is based on the following original publications, referred to in the text by their Roman numerals:


These publications have been reprinted with permission of their copyright holders. In addition, some unpublished material is presented.
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<th>Abbreviation</th>
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<tr>
<td>BNI</td>
<td>bladder neck incision</td>
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<td>CBC</td>
<td>cystometric bladder capacity</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>CIC</td>
<td>clean intermittent catheterization</td>
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<td>CMD</td>
<td>corticomedullary differentiation</td>
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<tr>
<td>CrEDTA</td>
<td>chromium ethylenediamine tetra-acetic acid</td>
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<tr>
<td>DMSA</td>
<td>dimercaptosuccinic acid</td>
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<td>DTPA</td>
<td>diethylenetriamine penta-acetic acid</td>
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<td>ESRD</td>
<td>end-stage renal disease</td>
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<td>GFR</td>
<td>glomerular filtration rate</td>
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<td>ICCS</td>
<td>International Children’s Continence Society</td>
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<td>IVU</td>
<td>intravenous urography</td>
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<td>LUT</td>
<td>lower urinary tract</td>
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<td>LUTD</td>
<td>lower urinary tract dysfunction</td>
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<td>LUTO</td>
<td>lower urinary tract obstruction</td>
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<td>MAG3</td>
<td>mercaptoacetyltryglycine</td>
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<td>Pmax det</td>
<td>maximal detrusor pressure</td>
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<td>PUV</td>
<td>posterior urethral valve(s)</td>
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<td>SE</td>
<td>standard error</td>
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<td>UDT</td>
<td>undescended testis</td>
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<td>US</td>
<td>ultrasonography</td>
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<td>UTI</td>
<td>urinary tract infection</td>
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<td>UTO</td>
<td>urinary tract obstruction</td>
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<td>UUT</td>
<td>upper urinary tract</td>
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<td>VCUG</td>
<td>voiding cystourethrogrammy</td>
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<td>VUR</td>
<td>vesicoureteral reflux</td>
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<td>VURD</td>
<td>syndrome of posterior urethral valves, unilateral reflux and renal dysplasia</td>
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INTRODUCTION

Posterior urethral valves (PUV) constitute a rather rare congenital disorder with membranous obstruction of the male posterior urethra. This form of infravesical obstruction is potentially seriously detrimental to the more proximal urinary system already prenatally. Consequences to bladder and kidneys may be irreversible, leading to chronic renal failure, end-stage renal disease and finally to death. Given its rarity, most medical professionals do not encounter many PUV patients, and few units have more than a limited experience in treating them. Nevertheless, in recent years mortality in PUV has been reported to have declined due to earlier diagnosis and referral to paediatric urological centers, improved instrumentation, achievements in pre- and postoperative management and greater experience in care of these severely ill patients (Cuckow 2006). As a consequence, there are now many patients requiring renal replacement therapy at a much earlier age (Dinneen and Duffy 1996, Cuckow 2006). Again paediatric surgeons and urologists treating these patients as a child rarely meet them in adulthood. Long-term outcomes of PUV are not properly known. In Finland, late outcomes of PUV patients have not been investigated. Systematic follow-up studies elsewhere are also lacking.

The aim of this study was to define the outcomes of PUV patients treated at Children’s Hospital, University of Helsinki, between 1953 and 2003, with a special emphasis on progression to ESRD and on risk factors for poor kidney outcome. In addition, the incidence of VUR and its association with primary kidney function and its spontaneous resolution are investigated. Moreover, the incidence of cryptorchidism and inguinal hernias and urinomas in PUV and the association with primary kidney function are explored. The associations of primary kidney function and voiding pressure and bladder capacity in infant patients are also evaluated.
REVIEW OF THE LITERATURE

HISTORY


The clinical importance of PUV was presumably not understood until Budd presented a case report in Lancet in 1840 (Budd 1840). A 16-year-old sailor was brought unconscious to hospital, dying there a few days later of uraemia and bilateral grave hydronephrosis. A membranous fold or valve of the posterior urethra and secondary changes in the bladder and UUT were described. Thirty years later, in 1870, Tolmatschew published autopsy findings of a newborn boy dying of renal failure. He also reviewed the previous literature (Tolmatschew 1870). He found two thin membranes attached to the anterior part of the verumontanum and urethral wall, one to the right and the other to the left, in a semicircular manner. Flow and pressure from the direction of the bladder caused swelling of the membranes, and obstruction of the lumen preventing the bladder from emptying. This author was also the first to discuss an embryological basis for the disorder.

In 1913, Young published a case report of successful management of PUV (Young et al. 1919). A 20-month-old boy had severe difficulties in passing urine, his bladder was distended and in cystography the proximal urethra was broad and an obstruction was present in the anterior part of the prostatic urethra. Suprapubic exploration was done and a vertical valve-like obstructive structure was felt, which was destroyed by diathermy. The boy’s general health had improved rapidly and voiding occurred without difficulty for one year. Unfortunately, the boy then died of diphtheria. In 1919, Young published his classical work in which, on the basis of his own and previous reports, he described 36 patients and classified valves into three different types (Young et al. 1919). In 1937, Campbell according to Hendren reported 63 cases and gradually thereafter more and larger materials were presented and finally it became apparent that urethral valves were not rare, but far more common than earlier suggested (Hendren 1971).
REVIEW OF THE LITERATURE

CLASSIFICATION

According to Young’s classification, there are three types of valves (Young et al. 1919). Type I is described as folds located distally from the verumontanum and fused anteriorly. Type II represents folds that run proximally between the verumontanum and bladder neck. Type III is illustrated as a diaphragm with an opening distal to the verumontanum (Young et al. 1919). This classification has, however, been questioned. Apparently type II is not obstructive and is generally considered to be hypertrophied superficial muscle and mucosa between the verumontanum and bladder neck. Differences between type I and III have also been re-evaluated. These have been argued to represent originally the same diaphragmatic type, which has converted to separate folds after urethral manipulation while inserting a catheter or an instrument (Robertson and Hayes 1969, Dewan 1993, Dinneen and Duffy 1996, Kajbafzadeh 2005, Cuckow 2006, Krishnan et al. 2006). Presman in his post-mortem study described five of his seven patents to have an iris or diaphragm-type obstruction (Presman 1961). Robertson and Hayes in autopsy of 20 deceased infants with congenital urethral obstruction removed the entire urinary tract including the penis en block. After detailed anatomical dissection in which special care was taken in removing the anterior wall of the prostatic urethra, bladder neck and bladder, they consistently found an oblique diaphragm with fibrous connective tissue membrane on each side with transitional epithelium and considered it to be responsible for the obstruction (Robertson and Hayes 1969). In accordance with this, Parkkulainen (1977) by endoscopic photographs documented all of his patients with a diaphragmatic type of obstruction initially. The term congenital obstructing posterior urethral membrane (COPUM), originally suggested by Dewan (1993), has been taken into use and deemed appropriate by some authors (Kajbafzadeh 2005, Krishnan et al. 2006, Hodges et al. 2009, Lazarus 2011). It has not, however, gained universal acceptance in clinical practice. Nevertheless, classification has been suggested to have no true value in clinical judgement with respect to management and prognosis of urethral obstruction (Kajbafzadeh 2005, Cuckow 2006).

EMBRYOLOGY

The cloaca divides into an anterior primitive urogenital sinus and a posterior rectum around 28 days after fertilization (Cuckow et al. 2001). The upper part of the primitive urogenital sinus forms the vesicourethral canal, which is the point of origin of the final bladder and proximal urethra. The distal part of primitive urogenital sinus will form the definitive urogenital sinus. In males, it gives rise
to the posterior urethra. The paired Wolffian ducts open at about six weeks to Müller’s tubercle, which will form the verumontanum in males. The bulbar urethra and the pendulous urethra are derived from the urethral plate on the ventral aspect of the genital tubercle (Cuckow et al. 2001, Krishnan et al. 2006).

The embryology of PUV is not known. Many theories have been presented. Currently, four major hypotheses prevail (Rattner et al. 1963, Friedland et al. 1977, Agarwal 1999, Kajbafzadeh 2005, Krishnan et al. 2006, Casella et al. 2012). Tolmatschew proposed that the valves were an overgrowth of normally existing folds and ridges (Tolmatschew 1870). Bazy in 1903 suggested that the remnants of the urogenital membrane were responsible for the valves (Friedland et al. 1977, Agarwal 1999, Krishnan et al. 2006). Lowsey in 1914 concluded that PUV were due to an anomaly of the Wolffian and Müllerian duct junction (Friedland et al. 1977, Agarwal 1999, Krishnan et al. 2006). According to Watson in 1922, persistence of the attachment of the verumontanum to the roof of the urethra and arrested fusion of the mucosal lining were responsible for PUV (Friedland et al. 1977, Agarwal 1999, Krishnan et al. 2006). Stephens suggested separate mechanisms for valves I and III. He supported the theory of Lowsey in type I and Bazy in type III obstruction (Krishnan et al. 2006). At present, the embryological mechanisms of PUV remain uncertain (Agarwal 1999, Kajbafzadeh 2005).

AETIOLOGY

The aetiology of posterior urethral valves is unknown. PUV is most commonly sporadic. However, familial cases have been reported in two successive generations, in siblings and in identical and fraternal twins (Schreuder et al. 2008, Morini et al. 2002, Weber et al. 2005). These findings may suggest some form of genetic background. Also recent analyses of congenital anomalies of the kidney and urinary tract (CAKUT) have proposed a common genetic mechanism (Pope et al. 1999, Weber et al. 2005, Song and Yosypiv 2011). However, the understanding of the molecular biology of human kidney and urinary tract organogenesis has thus far been insufficient (Song and Yosypiv 2011).

INCIDENCE

The incidence of PUV is estimated in general to be between 1/3000 and 1/8000 (Yohannes and Hanna 2002, Hodges et al. 2009), but figures indicating a rarer presentation, e.g. 1/25 000, have also been reported (Atwell 1983). In Oman, a general incidence of 1/2375 in newborn males has been observed (Rajab et al.
1996). In different districts of Oman, the incidences have ranged between 1/1700 and 1/5500. Interestingly, in a prospective prenatal US analysis 1/1285 infants was detected to have PUV (Gunn et al. 1995). Consequently, the true incidence of PUV at present is unknown, but the figure may be even higher than commonly assumed.

ASSOCIATED ANOMALIES

Posterior urethral valves are predominantly regarded as an isolated malformation. However, numerous congenital disorders in other organ systems have been reported in conjunction with PUV. These include single organ abnormalities and syndromes, virtually all of which are case reports. Rajab et al. (1996) managed to document in a detailed study of 84 PUV patients several urological, gastrointestinal and spinal anomalies, i.e. cryptorchidism, hypospadias, meatal stenosis, duplex kidney, ureteropelvic junction obstruction, dysplastic kidney, solitary kidney, ureteric diverticulum, inguinal hernia, anal stenosis, high anorectal anomaly, Hirschsprung disease, spina bifida, hemivertebra, scoliosis, congenital heart disease and mental retardation. Additional reported anomalies are anterior urethral valve (Rao et al. 2003, Bhagat et al. 2008), megalouretbra (Krueger and Churchill 1981), double urethra (Hendren 1971, Saigal et al. 2003), crossed renal ectopia (Hendren 1971), duplication of colon (Friedland et al. 1977) and imperforate anus (Hendren 1971, Shiraishi and Takihara 2004, Banever and Moriarty 2005). Syndromes include prune belly (Hendren 1971, Barker et al. 1993), Bardet-Biedl (Valavi et al. 2009), Beckwith-Wiedemann (Buyukcelik et al. 2005), Gorlin-Cohen (Vakalopoulos et al. 2012), de Goldenhaar (Palacios et al. 2007), Klinefelter (Nwosu and Hopkins 2008), Noonan (Barker et al. 1993), Ochoa (Weber et al. 2005) and Townes-Brocks (Weber et al. 2005).

The relationship between PUV and Down syndrome has been studied somewhat more closely. This chromosome aberration has been reported frequently among valve patients (Kupferman et al. 1996, 2009, Bielek et al. 1996, Hausmann and Landau 2002, Narasimhan and Gupta 2004, Culty et al. 2006, Ebert et al. 2008) and has been observed in 4-7% of patients with PUV (Kupferman et al. 1996, 2009 Bielek et al. 1996). Consistently, the risk of PUV in Down syndrome has been noted to be about 7-fold relative to those without the syndrome (Kupferman et al. 2009). No determinate explanation for the link between these two disorders has yet emerged.
CRYPTORCHIDISM

Cryptorchidism is usually reported to be found in 2-4% of full-term male infants (Hughes and Acerini 2008, Hutson et al. 2010). In a previous study comparing cryptorchidism in two Nordic countries, the prevalence at birth was 9.0% in Denmark and 2.4% in Finland (Boisen et al. 2004). The testis commonly descends at birth, but some spontaneous migration may still occur during the first months of postnatal life. At the age of one year, the incidence of undescended testes requiring surgery is on average 0.8-1% (Frey and Rajfer 1982, Hutson and Beasley 1992). In the aforementioned prospective two-centre study, the prevalence at three months was 1.9% in Denmark and 1.0% in Finland, and at 18 months the corresponding figures were 1.5% and 1.0% (Boisen et al. 2004). Descent of the testis is a complicated process with several factors participating. According to current evidence, normal testicular descent is believed to take place in two distinct phases, each having separate mechanisms (Mickel 1982, Hutson and Hasthorpe 2005, Virtanen et al. 2007, Hughes and Acerini 2008, Hutson et al. 2010). The transabdominal phase occurs at 8-15 weeks of foetal life and the inguinoscrotal phase at 25-35 weeks (Hutson and Hasthorpe 2005, Hughes and Acerini 2008, Hutson et al. 2010). The gubernaculum fixes to the cauda epididymis and anchors the testis to the inguinal region of the abdominal wall, and also participates in the canalicular and scrotal transition. Intra-abdominal pressure is believed to be important for normal descent (Backhouse 1982, Mickel 1982, Taskinen 1997, Hutson et al. 2010). Mechanical conditions and hormonal interactions are involved throughout the process. Insulin-like hormone 3, Leydig cell product, and anti-Müllerian hormone, Sertoli cell product have been suggested to be involved in the transabdominal phase (Hutson and Hasthorpe 2005, Hughes and Acerini 2008, Hutson et al. 2010). Androgens are required in the inguinoscrotal phase, and increased abdominal pressure presumably promotes the passage of the testis and epididymis through the canal (Backhouse 1982, Taskinen 1997, Hughes and Acerini 2008, Hutson et al. 2010). Genitofemoral nerve and its neurotransmitter may take part in this stage (Larkins et al. 1991, Hughes and Acerini 2008, Hutson et al. 2010). Lack of descent may be caused by hormonal defects or mechanical conditions. Prune belly syndrome and abdominal wall defects, bladder and cloacal extrophy, omphaloclele and gastrochisis have increased frequency of cryptorchidism, possibly secondary to bladder enlargement interfering with inguinal ring or changes in intra-abdominal pressure (Kaplan et al. 1986, Merksz and Toth 1990, Hutson and Beasley 1992, Koivusalo et al. 1998). Children with neural tube defects may have dysfunction of the genitofemoral nerve as a cause for retained testis (Hutson and Beasley 1992, Hutson et al. 2010). In patients with PUV, an incidence of cryptorchidism of up to 12% has been reported (Krueger et al. 1980b, Barker et al. 1993). The exact relationship between undescended testes and PUV and potential mechanisms have not been well established.
PATHOANATOMY

The valves of the posterior urethra cause anatomical obstruction of the urethral tube. The severity of the obstruction varies from one patient to another. The narrower the luminal hole in PUV, the greater the resistance to urine flow, probably resulting in secondary deleterious effects to the entire proximal urinary tract. Renal growth and function impairment in proportion to the severity and duration of obstruction have been noted in animal models (Chevalier 2008, Chevalier et al. 2010). There are, of course, many other mechanisms that exacerbate the renal damage. Typical findings of the urinary tract are dilatation and elongation of prostatic urethra, while the bladder neck remains rather narrow. Reflux to seminal vesicles, vasa deferentia and epididymis as well as to ureters may also take place. The bladder wall becomes trabeculated and thickens, and diverticulas may develop. Changes in the bladder wall constitute muscular hypertrophy, alterations in quality and amount of collagen, myosin and elastin resulting in a thick-walled non-compliant bladder (Rink and Mitchell 1990, Kim et al. 1991, Peters et al. 1992). Consequently, the bladder loses contractile strength and compliance and may develop high filling pressures. These changes may be irrecoverable and are responsible for the bladder dysfunction. Hypertrophy of detrusor muscle and elevated intravesical pressure disturbs ureterovesical junction anatomy and function. Higher pressure communicates back towards the kidney, inducing destruction of renal parenchyma, but also leading to malformation and reduction of the developing nephrons in utero (Peters 1997, Chevalier and Forbes 2008, Chevalier et al. 2010). Impaired nephrogenesis and nephron maturation in utero and in the infantile kidney are possible.

Response of the foetal kidney to obstruction appears to be distinct from that of the postnatal kidney (Peters 1997). Not only can foetal urinary tract obstruction (UTO) impact eventual renal function, but it appears to alter the very foundation of renal function by changing renal growth and differentiation (Peters 1997). In animal models, ureteral and urethral obstruction has been shown to produce hydronephrosis, renal cystic and dysplastic changes and impaired renal growth (Peters 1997, Chevalier et al. 2010). Tubular dilatation and apoptosis, glomerulotubular disconnection, reduction of the number of nephrons and interstitial fibrosis have been noted also in children with obstructive nephropathy (Chevalier et al. 2010). There is increasing evidence that in obstructive nephropathy destruction of the nephron begins in the renal tubule (Chevalier and Forbes 2008). In contrast, the proponents of bud theory tend to think that dysplastic alterations are defined as primary developmental malformations and are explained by inaccurate location of the ureteral bud and interaction with the renal blastema (Henneberry and Stephens 1980, Pope et al.
Accordingly, ectopic origins of ureteral buds lead to induction of defective or sparse mesenchyme of the tail end of the nephrogenic cord, with the result of dysplasia and hypoplasia. An abnormally lateral ureteral orifice in the bladder further predisposes to vesicoureteral reflux. In any case, renal dysplasia and hypoplasia in association with PUV are well-known major structural abnormalities. Polyuria is associated with nephrogenic diabetes insipidus caused by injury to the renal collecting tubules (Dinneen et al. 1995, Naghizadeh et al. 2005). Equally sustained polyuria and bladder overdistention are capable of leading to increased infravesical pressure and upper tract dilatation and renal injury (Koff et al. 2002). In addition, PUV patients may develop reflux nephropathy in the presence of VUR. Pyelonephritis, hyperinfiltration and glomerulosclerosis alone or with the other mechanisms may further damage the kidneys (Dinneen and Duffy 1996, Cuckow 2006).

**DIAGNOSIS**

**CLINICAL FEATURES**

After birth, boys with the worst obstruction generally present early (Pieretti 1993, Imaji and Dewan 2001). Severe oligohydramnios or anhydramnios predisposes to life-threatening pulmonary hypoplasia and respiratory distress and even to Potter sequence (Soo 2004, Cuckow 2006). Other prevailing symptoms and signs in neonates and infants are palpable urinary tracts, distended bladder, palpable kidneys, or urinoma, poor stream, dribbling, vomiting, failure to thrive, infectious complications, urinary tract infection and sepsis, and haematuria (Cuckow 2006).

Voiding symptoms, incontinence, haematuria and UTI have been observed to be the most common symptoms in late presenting PUV (Bomalaski et al. 1999, Yohannes and Hanna 2002, Schober et al. 2004). Adults have been reported to predominantly have voiding and ejaculatory dysfunction (Marsden 1969, Dutkiewicz 1994, Nguyen and Peters 1999).
Urinoma

Urinoma results from disruption of the urinary collecting system and escape of urine at any level from the calyx to the urethra (Titton et al. 2003). Most commonly, urine leaks result from blunt or penetrating trauma or increased back pressure caused by obstruction of the genitourinary system (Macpherson et al. 1986, Titton et al. 2003, Sancho Calvache and Pomares Amigó 2008). Urinary extravasation may initially be clinically occult and may manifest with delayed complications. The majority of neonate urinomas relate to lower urinary tract obstruction (LUTO), the commonest cause being PUV (Kay et al. 1980, Macpherson et al. 1986, Huang and Cheng 1990). The supposed mechanisms to the escape of urine in infravesical obstruction are rupture of thinned renal parenchyma, leak from calcyleal fornices, bladder rupture and transudation of urine (Greenfield et al. 1982, Patil et al. 2003). Perirenal urinoma and urinary ascites are the most often reported sequelae. Urinothorax is believed to result from retroperitoneal or transdiaphragmatic shift of retroperitoneal or intraperitoneal collection into the pleural space (Garcia-Pachon and Padilla-Navas 2004, Lee et al. 2005, Sancho Calvache and Pomares Amigó 2008). Urinomas have been reported to occur in 1-8.5% of PUV patients (Greenfield et al. 1982, Rittenberg et al. 1988, Patil et al. 2003). Because of the small patient numbers in individual reports, the significance of urinoma in this disorder is in many ways unclear. The clinical characteristics of PUV patients with or without urinoma have not earlier been thoroughly compared.

ANTENATAL DIAGNOSIS

In congenital obstructive disease, the nature and location of the obstruction and its impact on the upper urinary tract must be determined. During the last decades US has become an essential tool in maternal care and foetal evaluation. The male foetus showing bilateral hydronephrosis with a constantly distended and thick-walled bladder is known to be suggestive for LUTO, and thus, for PUV (Agarwal 1999). A dilated prostatic urethra can occasionally be seen and a “keyhole sign”, representing an enlarged bladder and dilated proximal urethra, adds to the reliability of a diagnosis of urethral obstruction (Vanderheyden et al. 2003, Quintero 2005). However, a definite diagnosis of the underlying aetiology causing LUTO is deemed impossible using prenatal US alone (Thomas 2001, Lissauer et al. 2007, Ruano 2011).

The fast scanning technique of magnetic resonance imaging offers a valuable aid to US of the foetal urinary tract if resolution is impaired because of severe oligohydramnion or for other reasons (Poutamo et al. 2000, Payabvash et al. 2008, Ruano 2011).
POSTNATAL DIAGNOSIS

IMAGING

Ultrasound is, in most cases, the primary imaging method. It detects kidney size and confirms hydronephrosis and may suggest the cause and even the anatomical site of the obstruction. US can also differentiate parenchymal changes according to alterations in echogenicity, is easily available and allows repeated investigations without radiation.

Voiding cystourethrography (VCUG) locates and demonstrates the obstruction exactly and is the most valuable radiological examination. It is the diagnostic method of choice to image the bladder and urethra. VCUG also identifies preobstructive secondary changes in the urinary tract and registers vesicoureteral reflux. Moreover, it detects and grades VUR (Ismaili et al. 2006, Mathews et al. 2009).

![Ultrasound: Hydroureteronephrosis in a 5-year-old boy with UTI. Hydronephrosis (upper arrow) and wide ureter (lower arrow).](image)

**Figure 1.** Ultrasound: Hydroureteronephrosis in a 5-year-old boy with UTI. Hydronephrosis (upper arrow) and wide ureter (lower arrow).
REVIEW OF THE LITERATURE

Figure 2. Ultrasound: Thick trabeculated bladder wall (upper arrow) and megaureters (lower arrows) suggestive of PUV in a 5-year-old boy with UTI.

Figure 3. Voiding cystourethrography: Trabeculated bladder (triangle), high-grade vesicoureteral reflux (upper star), prominent bladder neck (upper arrow), dilated posterior urethra (lower star) and PUV (lower arrow).
Radionuclide cystography (RNC) reliably detects VUR, but does not allow morphological changes in the urinary tract to be evaluated. RNC is usually reserved for follow-up studies of VUR (Cooper 2009).

Mercaptoacetyltriglycine (MAG3), diethylenetriamine penta-acetic acid (DTPA) and dimercaptosuccinic acid (DMSA) scintigraphy are sensitive to renal dysplasia and scarring, and also allow evaluation of relative renal function. MAG3 and DTPA have additional value in judging co-existing obstructive states of UUT.

Intravenous urography (IVU) has historically been the major imaging technique and is capable of demonstrating the anatomy of UUT in the presence of reasonable renal function. Currently, it has been replaced by modern scintigraphy and US (Gordon et al. 1987, Chevalier 2008).

Magnetic resonance voiding cystography (MRVC) and magnetic resonance urography (MRU) are not at present widely available. They are, however, safe methods with no ionizing radiation and are potential alternatives as primary imaging modalities in evaluation of UTO (Leppert et al. 2002, Perez-Brayfield et al. 2003, Lee et al. 2005, Chevalier 2008).

URETHROCYSTOSCOPY

Urethrocystoscopy enables identification of the valves. Urethroscopy allows the valves to be visualized directly. Bladder wall trabeculation and diverticula and the localization and shape of ureteric orifices can also be viewed and evaluated endoscopically.

URODYNAMIC EVALUATION OF BLADDER DYSFUNCTION

Lower urinary tract dysfunction (LUTD) is frequent in boys with PUV. Of those referred to urodynamic evaluation, over 70% have been reported to have severe dysfunction (Bauer et al. 1979, Parkhouse and Woodhouse 1990, Peters et al. 1990, Holmdahl et al. 1995, De Gennaro et al. 2000). In addition, a non-compliant thick-walled bladder, incontinence and nephrogenic diabetes insipidus with persistent UUT dilatation following valve ablation have been described and collectively are referred to as ‘valve bladder syndrome’ (Glassberg 2001, Koff et al. 2002, Taskinen et al. 2012). However, Koff et al. (2002) noted small, hypercontractile, poorly compliant bladders to not only reach normal capacity with age but become overdistended. According to Koff et al., valve bladder syndrome results from sustained bladder overdistention that is caused by a combination of polyuria, impaired bladder sensation and high residual urine volume (Koff et al. 2002).
In 2006, the International Children’s Continence Society (ICCS) updated the standardized terminology of LUT function in children (Nevéus et al. 2006). According to the modified ICCS terminology, the three most commonly found urodynamic patterns in patients with PUV are as follows: 1. detrusor overactivity, 2. low bladder compliance and 3. myogenic failure (detrusor underactivity) (Peters et al. 1990, Holmdahl et al. 1995, De Gennaro et al. 2000, Lopez Pereira et al. 2002, Kajbafzadeh et al. 2007). The incidence of these findings has been observed to vary and overlap between the groups, presumably related to the age of the patient. In PUV patients, detrusor overactivity, which is frequent in infancy, has a tendency to become underactive with age. Accordingly, hypocontractibility and myogenic failure have been reported in older children. Successive increase in bladder capacity is suspected to be accompanied by a risk for overdistention (Holmdahl et al. 1997, De Gennaro et al. 2000, Kajbafzadeh et al. 2007). This concept of changing urodynamic patterns is not, however, universally accepted.

In infants, at the time of diagnosis of PUV, bladder function has rarely been evaluated, and the association between voiding pressures and kidney function is unclear.

MANAGEMENT

ANTENATAL MANAGEMENT

Foetal surgery for treatment of obstructive uropathy was first reported in humans at the University of California, San Francisco, in 1981 (Holmes et al. 2001). In this series, such procedures as placement of vesicoamniotic shunt, bladder marsupialization, ablation of valves and cutaneous ureterostomies were utilized (Holmes et al. 2001). Open foetal surgery has since been abandoned almost completely because of increased maternal and foetal risks. Alternative minimally invasive approaches have been developed instead, with the rationale of restoring the amniotic fluid, thus preventing lung hypoplasia, and decompressing the urinary tract to protect against renal impairment (Lissauer et al. 2007, Ruano 2011, Casella et al. 2012). The most common procedure to relieve LUTO is to place a stent, a percutaneous vesicoamniotic shunt. Another option is foetal endoscopy and treatment of valves. It has been postulated that this latter procedure allows restoration of normal foetal bladder dynamics (Quintero et al. 2000, Lissauer et al. 2007). However, thus far, human studies have failed to show any benefit of antenatal intervention for preserving normal renal function (Morris et al. 2010, Casella et al. 2012). The overall perinatal survival rate after shunt placement was only 47% and shunt-related complications were 45% in a report summarizing five
larger series comprising 169 patients in total (Agarwal and Fisk 2001). Also in foetal cystoscopy an average of 50% survival has been reported in a collected series (Ruano 2011). Antenatal management has not attained wide acceptance to date. Since the amniotic fluid level is maintained by foetal urine production after around the 16th week of gestation, irreparable damage may have occurred in the foetus before critical obstruction is noted (Holmes et al. 2001). Antenatal management is considered experimental and is hampered by severe complications, including preterm labour and foetal death. It has been proposed, however, that the future of valve therapy may well lie in foetal surgery, as the equipment and techniques used to treat foetal urinary tract obstruction evolve (Hodges et al. 2009).

**POSTNATAL MANAGEMENT**

Laboratory examinations include assessment of renal function and UTI. Microscopic examination and culture of urine are routine. Renal function is estimated by measuring serum creatinine, and later glomerular filtration rate (GFR) is determined more accurately by creatinine clearance or chromium ethylenediamine tetra-acetic acid (CrEDTA) values (Ylinen 2004, Kajbafzadeh 2005).

Bladder drainage is established by either urethral or suprapubic catheter. Simultaneous correction of electrolyte and acid-base imbalance and control over infection are crucial. Electrolyte and acid-base balance are monitored frequently. Hyperkalemic acidosis is a known common serious sequela (Dinneen and Duffy 1996, Kajbafzadeh 2005).

**Valve ablation**

Ablation of valves as a surgical treatment is the preferred option as soon as the child’s overall condition has stabilized. Most paediatric urologists agree that endoscopic valve resection is the preferred method for removing posterior urethral valves (Hulbert and Duckett 1988, Lopez Pereira et al. 2004, Sarhan et al. 2010, Smeulders et al. 2011).

The endoscopic approach allows identification and destruction of the valves under direct vision. This can be performed in a retrograde or antegrade fashion, the former being more typical (Hulbert and Duckett 1988, Yohannes and Hanna 2002, Cuckow 2006). The narrowest point of a child’s urethra is the meatus. This may be gently dilated to allow an appropriate-sized cystoscope to be introduced. However, it is important not to over-dilate the urethra by using a larger cystoscope than the urethra can accept (Agarwal 1999). The valves can be abolished by the preferred instrumentation available, e.g. resectoscope loop, cutting or electrode

Bladder neck incision (BNI) is considered to be seldom justified, and most authors advocate avoiding BNI to minimize bladder neck contracture and incontinence (Yohannes and Hanna 2002). However, some recent reports have stated that a degree of bladder neck hypertrophy may accompany valvular obstruction (Androulakakis et al. 2005, Kajbafzadeh et al. 2007). Accordingly, BNI in conjunction with valve resection has again been suggested to improve bladder dynamics (Androulakakis et al. 2005, Kajbafzadeh et al. 2007, Lazarus 2011). Also BNI has been recommended in late presenting adult patients with persistent severe bladder neck contracture after resection of PUV (Culty et al. 2006).

**Urinary diversion**

Urinary diversion has had priority in management of infants with a urethra that is too small to allow passage of instruments or in the critically ill with resistant urinary infection and insufficient drainage of the UUT with rising plasma creatinine values after ablation of valves (Agarwal 1999, Nasir et al. 2011). Krueger and associates have shown that those neonates and infants with primarily upper tract diversion compared with primary valve resection had better growth and better renal function at an average follow-up of 7.4 years (Krueger et al. 1980a, Churchill et al. 1983). By contrast, temporary or permanent reduction of bladder volume was seen in 15 patients with defunctionalized bladder secondary to cutaneous ureterostomy diversion in the report of Lome et al. (1972). Probably these latter findings and the development of infant instruments and neonatal intensive care lead to preference of straightforward endoscopic ablation without diversion. Smith et al. (1996) in a series of 100 patients concluded that PUV should be treated with primary valve ablation and vesicostomy should be reserved for those in whom ablation is technically impossible. They judged high diversion as disadvantageous. Much of the criticism against supravesical urinary diversions was based on modifications where the bladder was defunctionalized (Liard et al. 2000). However, alternative techniques, such as Sober pelviureterostomy, ureteral chimney and ring ureterostomy, allow bladder cycling. Recently Lopez Pereira and associates (2003) observed again that the patients treated with early temporary pyelo-ureterostomy had a better renal function in follow-up. Benefits of cutaneous supravesical diversion were obvious, and justification for temporary urinary diversion in order to improve renal function prognosis in some particular cases was affirmed (Lopez Pereira et al. 2003, 2004).
**Vesicoureteral reflux and auxiliary surgery**

Vesicoureteral reflux, retrograde flow of urine from the bladder into the ureter, is generally estimated to occur in 1-3% of children (Fanos and Cataldi 2004, Cooper 2009). However, also much higher figures have been proposed (Venhola 2011). The estimation of the severity of VUR is determined according to VCUG, which is regarded as the gold standard for imaging reflux (Ismaili et al. 2006, Mathews et al. 2009). Clinicians have been advised to use the well-established grading system adopted by the International Reflux Study Committee (IRSC), which is based on the classification originally presented by Heikel and Parkkulainen (1966) (Tekgül et al. 2012). Grade I visualizes the escape of contrast medium into the ureter only and grade II into an anatomically normal pyelocalyceal system. Grade III constitutes reflux to the dilated collecting system, and in grade IV there is more pronounced dilatation with blunting of the calyces and tortuosity of the ureter. Grade V represents massive reflux with gross dilatation and deformation of the collective system and ureter (Heikel and Parkkulainen 1966, Tekgül et al. 2012).

Primary VUR is presumed to be related to the anomalously short intravesical tunnel at the ureterovesical junction or to LUTD (Cooper 2009, Tekgül et al. 2012). The demonstration of spontaneous resolution of primary VUR has led to the concept of initial conservative management and limitation of surgical correction to those patients who fail to recover with these non-operative regimens (Mathews et al. 2009, Tekgül et al. 2012).

PUV are accompanied by VUR with reported incidences usually between 26% and 72% (Dinneen and Duffy 1996). VUR in these patients is considered to be secondary to the increased infravesical pressure and loss of ureterovesical junction competence (Jaureguizar et al. 2002, Hassan et al. 2003, Lopez Pereira et al. 2004). Dilated UUT combined with persistent UTI has been reported to be associated with high morbidity and mortality in the past (Hendren 1971, Williams et al. 1973). Early ureterovesical reconstruction, reimplantation and remodelling of ureters have been proposed in cases with gross dilatation of the upper urinary tract (Hendren 1971, Bjordal et al. 1978, Casale 1990). Recently El-Sherbiny and associates reported 20% of their patients to have undergone ureteroneocystotomy. However, 26% had postoperative VUR and 4% ureterovesical junction obstruction as a complication to the procedure (El-Sherbiny et al. 2002). Currently, the majority of paediatric urologists advocate observational regimens after release of the distal obstruction (Connor and Burbige 1990, Smith et al. 1996, Farhat et al. 2000). However, there are few studies concerning resolution of VUR after ablation of urethral valves. VUR has been reported to subside spontaneously in 27-79% of refluxing ureters in a period of 2 weeks to more than one year after ablation of valves (Johnston and Kulatilake 1971, Johnston 1979, Scott 1985, Lal et al. 1998b, Farhat et al. 2000, Priti et al. 2004). True long-term studies concerning the resolution of VUR and
renal function in PUV patients are, however, scarce. Reflux has been noted to be associated with renal failure, especially in cases of bilateral reflux (Johnston 1979, Tejani et al. 1986, Parkhouse et al. 1988, Denes et al. 1997, Oliveira et al. 2002). On the other hand, opposing views have been presented, and unilateral reflux with the ipsilateral non-functioning kidney has been suggested to protect contralateral kidney function (Hoover and Duckett 1982, Greenfield et al. 1983, Donnelly et al. 1997, Oliveira et al. 2002). Nephrectomy has been adopted in recurrent or resistant UTI in patients with a non-functioning kidney. Previously, 17-19% of valve patients have undergone removal of a non-functioning kidney (Cuckow et al. 1997, Atwell 1983, Holmdahl and Sillén 2005). However, the significance and proper management of VUR in boys with PUV remain in many respects controversial.

OUTCOMES

SURVIVAL

During the early years of management primary mortality was high. The mortality rates particularly among those presenting as neonates were rather miserable. Johnston and Kulatilake reported rates of 50%, Williams 52% and Retief and Shippel 75% in patients presented under the age of one month (Johnston and Kulatilake 1971, Williams et al. 1973, Retief and Shippel 1976). The overall mortality in these series was 32%, 16% and 33%, respectively. Egami and Smith (1981) reported 49% neonatal mortality and 21% overall mortality. Cass and Stephens (1974) witnessed a dramatic decline in neonatal and overall mortality from 78% to 15% and 22% to 6%, respectively, from 1950-1961 to 1962-1972. Consistently, Churchill and associates (1983) reported a profound reduction in overall mortality from 25% in 1957-1968 to 3% in 1969-1978. In the work of Cass and Stephens, deaths occurred during initial hospitalization, and in the study of Churchill and associates, with one exception, within 12 months of diagnosis. During the 1980s mortality of 0% from the latter institution was reported (Churchill et al. 1990). Later, mortality figures of 0-2% at many tertiary referral children’s hospitals have been published (Dinneen and Duffy 1996).

Improvement is concluded to be related to better awareness of the valves, earlier diagnosis and referral, advancements in neonatal intensive care, better antibiotics, more sophisticated surgical instruments and improvements in the management of neonates and infants with acute and chronic renal failure (Churchill et al. 1983, Cuckow 2006).
POSTOPERATIVE MORBIDITY AND COMPLICATIONS

The incidence of complications after valve ablation has typically ranged between 5% and 28% (Yohannes and Hanna 2002, Kajbafzadeh 2005).

Urethral stricture after ablation of valves has occurred in 8-28% of patients (Churchill et al. 1983). Since the early years of management, these figures seem to have declined to 4-8% (Crooks 1982, Lal et al. 1998a, Sudarsanan et al. 2009). Currently, the prevalence of urethral stricture has been observed to be very low, 2% (Sarhan et al. 2010) or even 0% (Bhatnagar et al. 2000, Chertin et al. 2002, Caione and Nappo 2011).

Residual valves necessitating second ablation have been reported in 1-29% of patients (Kimbrough and Wyker 1977, Bhatnagar et al. 2000, Chertin et al. 2002, Bani Hani et al. 2006, Sudarsanan et al. 2009, Sarhan et al. 2010, Babu and Kumar 2013).

Other reported complications include postoperative urinary retention, postoperative urethral bleeding, intraperitoneal leak of the irrigating fluid, urinary extravasation, UTI, epididymitis, urethral diverticulum and bladder neck contracture (Androulakakis et al. 2005, Sinha et al 2009, Sarhan et al. 2010).

PROGRESSION TO END-STAGE RENAL DISEASE

Long-term outcome of posterior urethral valves has not been properly clarified. Early mortality has declined and consistently more patients with severe renal injury have survived (Dinneen and Duffy 1996). In accordance with this, many children with PUV develop ESRD, chronic irreversible renal failure, and require dialysis and renal transplantation. Of PUV patients, 5-64% end up with ESRD during childhood or adolescence (Roth et al. 2001). In paediatric age groups, the most common ages to develop ESRD have been concluded to be the first year of life and adolescence (Smith et al. 1996). The follow-up in that study was not, however, extended to adulthood. Some patients do not develop chronic renal failure and ESRD until adulthood (Uehling 1980, Parkhouse et al. 1988, Holmdahl and Sillén 2005). Because late renal outcome has not been systematically analysed, the true late renal outcome is unknown.

PREDICTIVE FACTORS FOR END-STAGE RENAL DISEASE

Traditionally, age at presentation, early serum creatinine values and reflux have been considered major risk factors for renal outcome in patients with PUV. Various other parameters have also been suggested to have an impact. These
include pulmonary hypoplasia, urinary ascites, UTI, LUTD, renal echogenicity and proteinuria. Evidence for these variables remains inconclusive.

**Age at presentation**

Early age at presentation is mostly regarded as a risk for later renal failure. Diagnosis before one year of age is a negative predictive factor of renal failure (Parkhouse et al. 1988, Kibar et al. 2011). Delayed presentation has historically been associated with a more benign clinical course (Hendren 1971, Parkhouse et al. 1988, Pieretti 1993). In contrast, a number of studies from several institutions have revealed that impaired renal function is associated with delayed diagnosis or that there is no difference among those diagnosed early or late (Tejani et al. 1986, El-Sherbiny et al. 2002, Zylan et al. 2006, Ansari et al. 2010, Engel et al. 2011).

Prenatal diagnosis has been anticipated to be beneficial for infants with PUV by facilitating early postnatal decompression, shortening the duration of obstruction and minimizing the risks of infective renal damage (Kousidis et al. 2008, Thomas 2010). Accordingly, Dinneen et al. (1993) reported better renal function in the antenatally diagnosed group during the first year of life. Reinberg et al. (1992) failed to demonstrate clinical improvement in prenatally detected PUV relative to those with postnatal diagnosis. Moreover, Jee et al. (1993) found in their study that the outcome was worse in prenatally detected cases.

**Serum creatinine values**

High serum creatinine levels at presentation and especially during the first year after valve resection have been shown to be signs of poor renal prognosis in studies with a short or intermediate follow-up. Recently, Sarhan et al. (2010) noted a clear prognostic relation between initial serum creatinine and future renal function after a mean follow-up of 4.4 years. In accordance with this, high serum creatinine levels at diagnosis and during the first year after valve resection indicated poor prognosis in some previous reports (Uehling 1980, Denes et al. 1997, Drozdz et al. 1998, Oliveira et al. 2002, DeFoor et al. 2008). Also postoperative nadir creatinine and serum creatinine at the age of one year have been shown to have prognostic significance (Denes et al. 1997, Drozdz et al. 1998, Ylinen et al. 2004, Sarhan et al. 2010). In addition, GFR initially and at the age of one year has been noted to have predictive value (Scott 1985, Lopez Pereira et al. 2003, Sarhan et al. 2011). In contrast, Bajpai et al. (2001) and Engel et al. (2011) in recent studies found no significant correlations with initial serum creatinine and progression to chronic renal failure. Nevertheless, normal creatinine values at presentation
do not exclude the possibility for later ESRD (Denes et al. 1997, Roth et al. 2001, Kousidis et al. 2008).

**Vesicoureteral reflux**


Unilateral reflux, especially with an ipsilateral non-functioning kidney, has been suggested to protect contralateral function. Hoover and Duckett (1982) postulated that this association spares the contralateral non-refluxing kidney and ultimately renal function. Rittenberg et al. (1988) recognized this linkage of PUV, unilateral VUR and renal dysplasia (VURD), and presented two additional “pop-off” mechanisms in PUV: urinoma and large congenital bladder diverticulum. These have been the topic of ample discussions in paediatric urological literature (Fernbach et al. 1990, Donnelly et al. 1997, Claahsen-van der Grinten et al. 2002, Oliveira et al. 2002, Lee et al. 2005, Wells 2010). In contrast, children with VURD in recent studies were observed to have impaired renal function (Cuckow et al. 1997, Narasimhan et al. 2005). This is obviously not in line with a protective effect of VUR. Sarhan et al. (2011) did not find statistical significance between the presence or absence of these pop-off mechanisms and final renal outcome.

**Urinary tract infection**

UTIs have been associated with poor outcome and renal impairment in previous reports (Denes et al. 1997, Roth et al. 2001, Holmdahl and Sillén 2005, Narasimhan et al. 2005). Pyelonephritis is supposed to augment renal damage (Tejani et al. 1986). Ansari et al. (2010) and Engel et al. (2011) did not find clinical UTIs to be associated with chronic kidney disease progression. Denes et al. (1997) and Narasimhan et al. (2005), in turn, noted postoperative UTIs to have an adverse effect on later renal function. Pohl et al. (2012) reported that recurrent, i.e. more than three, UTIs are a risk factor for renal impairment.
REVIEW OF THE LITERATURE

**Incontinence and bladder dysfunction**

Incontinence and LUTD have been reported to predict poor renal outcome in urethral valve patients in some reports. Parkhouse et al. (1988) observed that children with PUV with persisting day-time urinary incontinence at the age of five years had a worse renal function relative to those who were continent. Urinary incontinence and LUTD have also been reported to predict poor kidney function in PUV patients by others (Lopez Pereira et al. 2002, Holmdahl and Sillén 2005, DeFoor et al. 2008, Ansari et al. 2010). Interestingly, Sarhan et al. (2008) did not find bladder dysfunction to affect final renal outcome. No relation between urinary incontinence or bladder dysfunction and final renal outcome was seen in some recent reports (Sarhan et al. 2008, Kousidis et al. 2008, Engel et al. 2011).

**Proteinuria**

Parkhouse et al. (1988) and Lopez Pereira et al. (2003) identified proteinuria to be associated with poor long-term outcome.

**Other renal changes**

US has been proposed to help in identifying patients with the highest risk for renal failure. Pohl et al. (2012) reported elevated echogenicity and pathological corticomedullary differentiation (CMD) as a significant risk factors for decreased GFR. Normal renal echogenicity and CMD were considered useful in predicting good outcome (Duel et al. 1998, Sarhan et al. 2011). However, in some studies abnormal renal parenchymal echogenicity has been found to be relatively insensitive and poorly specific in predicting renal failure (Duel et al. 1998, Lopez Pereira et al. 2003, Sarhan et al. 2011).

**RENAL TRANSPLANTATION**

To prevent further kidney damage in PUV patients, proper auxiliary therapy is of particular importance. With progression to ESRD, renal transplantation has been shown to offer good functional outcome even in patients with PUV (Bryant et al. 1991, Otukesh et al. 2008, Kamal et al. 2011). In addition, with adequate treatment the craft survival currently seems to be similar in PUV patients and non-urological patients (Otukesh et al. 2008, Kamal et al. 2011, Jesus and Pippi Salle 2015). However, a tendency for more frequent urinary tract infections and operative complications, such as urinary leakage and ureteral obstruction, in PUV patients has been reported (Kamal et al. 2011).
AIMS OF THE STUDY

PUV is a disorder that can cause serious consequences to the bladder and upper urinary tract. Despite advances in diagnosis and management, many patients progress to ESRD. Although it is a rather rare disorder, it is one of the most common causes for renal transplantations in childhood. The ultimate aim of this study is to improve awareness of PUV. By investigating risk factors, the prognosis and quality of life of PUV patients can be improved.

Specific aims were as follows:

1. to determine the progression of PUV to ESRD and the need for renal transplantations
2. to determine risk factors for poor kidney outcome
3. to determine the incidence of VUR in PUV patients and its association with primary kidney function and the spontaneous resolution of VUR
4. to determine the incidence of cryptorchidism and inguinal hernias in PUV and the association with primary kidney function
5. to evaluate the association of primary kidney function with voiding pressure and bladder capacity in infant patients
PATIENTS AND METHODS

PATIENTS AND CONTROLS

The hospital records of all patients treated for posterior urethral valves at Children’s Hospital, University of Helsinki, Helsinki, Finland, between 1953 and 2003 were reviewed retrospectively. The diagnosis of PUV was based on voiding cystourethrogramy and confirmed by urethral endoscopy or open surgery in early series. Two hundred patients were identified and serve as the basis for Studies I, II, IV and V. In addition, the hospital database for urodynamic studies and the case note archive were retrospectively reviewed for PUV patients from 1994 to 2007. Twenty-five infant patients born between 1994 and 2007 met the criteria of age less than 12 months at the time of valve ablation and a urodynamic study within 15 days of the procedure, and were evaluated for voiding pressure and bladder capacity (III). These results were compared with a historical institutional control group, comprising male infants with a febrile UTI before the urodynamic investigation (Taskinen and Rintala 2007). Data on the deceased patients of the study material were sought from the Finnish Population Register Centre if the demise was not registered in hospital records. Patients undergoing dialysis treatment or transplantation were sought from patient records and the Finnish Kidney Transplantation Registry. Data of study patients were retrospectively collected with special emphasis on age and mode at presentation, associated diseases, existence of urinomas, VUR, surgical treatment, early and late mortality and progression to ESRD. Serum creatinine values at presentation and at follow-up visits and primary scintigraphy were registered for evaluation of renal function.

METHODS

CRYPTORCHIDISM AND INGUINAL HERNIAS (I)

Information concerning kidney function, VUR, and cryptorchidism and inguinal hernias was collected from hospital records. Testicular descent status and inguinal hernias were reported in 192 patients. Serum creatinine values at diagnosis and 6 months postoperatively, primary renal split function and VUR in patients with undescended testes (UDT) and inguinal hernia were compared with those of patients without cryptorchidism and hernias.
URINOMAS (II)

In 196 patients with sufficient data in patient charts and radiology reports at the time of presentation, serum creatinine values at the time of diagnosis and 6 months postoperatively, primary renal split function and VUR were registered. Patients with urinoma were compared with patients of a similar age at presentation but without urinoma. Also incidence of end-stage renal failure during childhood was compared in both patient groups.

PRIMARY VOIDING PRESSURES AND KIDNEY FUNCTION IN INFANTS (III)

In the urodynamic evaluation of 25 infant patients, abdominal and bladder pressures and subtracted detrusor pressure were measured simultaneously using Ch4 feeding tubes and computerized equipment (Menuet, Dantec Co, Copenhagen, Denmark). Bladder filling was performed via a separate Ch4 feeding tube in 17 cases and a Ch5 suprapubic catheter in 8 patients. The first urodynamic evaluation was performed in 6 patients at a median of 3 (range 2 to 6) days before and in 19 patients at 2 (range 0 to 15) days after valve ablation. In 17 patients, the urodynamic studies were repeated after a median of 1.7 (range 1 to 3.5) months and after a median of 12.6 (range 6.7 to 20) months.

Pmax det during voiding and CBC were compared with those of earlier institutional control group. The median age of the control group was 3.3 (range 1.5-9.6) months. The urodynamic techniques in the control patients were similar to those in the present study. The voiding pressures were also compared with previous published reports of normal infants and infant patients with variable pathologies.

The serum creatinine values at presentation as well as at 6 and 12 months after valve ablation were compared with the urodynamic parameters. Also the occurrence of VUR and scintigraphic renal split function were compared with the urodynamic parameters.

VESICOURETERAL REFLUX (IV)

Sufficient data to confirm VUR at presentation were available for 197 patients. In patients with VUR, the serum creatinine values at the time of diagnosis, at 6 and 12 months and at 5 to 7 years postoperatively, and primary renal split function were compared with those of patients without VUR. Also the incidence of end-stage renal disease during childhood was compared in the same patient groups.

The management and resolution of VUR were analysed in the whole series. Additionally, in patients born between 1980 and 2003 and initially treated at Children’s Hospital, University of Helsinki, the spontaneous resolution of VUR was analysed separately in detail.
PATIENTS AND METHODS

LONG-TERM RISK OF END-STAGE RENAL DISEASE (V)

Seven patients died early and their renal function was not determined. In the remaining 193 patients, the age and mode at presentation, the existence of VUR, urinomas and pneumothorax, and serum creatinine values at presentation and during the first year after the release of the obstruction as well as UTIs and incontinence during childhood were registered and compared with kidney outcome. Progression to end-stage renal failure was assessed. The associations between primary serum creatinine values and patient age at onset of ESRD were analysed. Patients born before and after 1982, which was the threshold for prenatal ultrasound studies in this series, were also compared.

STATISTICS

The Mann-Whitney test was used to compare continuous variables between two groups (I – V) and the Kruskal-Wallis test between three groups (IV). Fisher’s exact test was used to compare categorical variables (I, II, IV, V). Wilcoxon signed-rank test was used to compare repeated measurements (III). Regression analysis was performed to evaluate associations between urodynamic parameters and serum creatinine levels or kidney split function and to test the association between the lowest serum creatinine during the first year after diagnosis and age at ESRD (III, V). Kaplan-Meier analysis was performed to evaluate the development of ESRD (V).

Statistical analyses were carried out with the Statview software program (Statview® 5.0.1, SAS Institute Inc. Cary, North Carolina, USA). Significance was set at p<0.05.

ETHICS

The study protocol was approved by the Ethics Committee of Children’s Hospital and the Ethics Committee for Paediatrics, Adolescent Medicine and Psychiatry, University of Helsinki, Finland.
RESULTS

CRYPTORCHIDISM AND INGUINAL HERNIAS (I)

Cryptorchidism requiring operation was found in 31 (16%) of 192 patients, in 22 (11%) unilaterally and in 9 (5%) bilaterally. In these 31 patients, the incidence of undescended testis was 16 (95% CI 11-21) -fold higher than in the normal Finnish population (Boisen et al. 2004). Right and left testicle in unilateral cryptorchidism was observed to have been retained equally often, in 11 patients each. In 29 patients, the location of the cryptorchid testis was reported, 25 testes were inguinal, 2 were suprascrotal and 2 were high scrotal. Tendency towards a more severe form of PUV in patients with cryptorchidism was observed, as their serum creatinine levels were higher and they more often had poor kidney function on one side than patients without cryptorchidism (Tables 1 and 2). In addition, UDT was more common among patients presenting earlier. Cryptorchidism was detected in 14 (27%) of 52 patients with a neonatal diagnosis of PUV and in 18 (14%) of the 130 patients with a later diagnosis (p=0.027). Of the 28 patients with an antenatal diagnosis of PUV, cryptorchidism was found in 3 (11%). Concomitant VUR was equally common in patients with and without cryptorchidism (22/31, 71% vs. 103/158, 65%, respectively; p=0.679).

Inguinal hernias requiring operation not related to ipsilateral UDT were observed in 21 (11%) of 192 patients. Hernias were unilateral in 14 patients, 10 on the right side and 4 on the left, and bilateral in 7 patients. Hernias were found in 18 (11%) of 161 patients without cryptorchidism and in 3 (10%) of 31 patients with UDT on the contralateral side. Higher serum creatinine levels at presentation were also measured in patients with inguinal hernias relative to those without hernias (mean 178 ±137 µmol/L vs. 110± 94 µmol/L, respectively, p=0.002; median 173, range 38-593 vs. 80, range 14-488, p= 0.003). However, serum creatinine levels 6 months later and patient age at diagnosis were even in patients with and without hernias.
RESULTS

Table 1. Age at presentation and differential function of worse kidney in cryptorchid and non-cryptorchid PUV patients.

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<td>Non-cryptorchid*</td>
<td>136</td>
<td>3.14± 4.41</td>
<td>0.70</td>
<td>0–25.52</td>
<td></td>
</tr>
<tr>
<td>Cryptorchid</td>
<td>28</td>
<td>1.49± 3.06</td>
<td>0.11</td>
<td>0–11.93</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Differential function of the worse kidney (%)**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean± SD</th>
<th>Median</th>
<th>Range</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cryptorchid</td>
<td>84</td>
<td>32± 17</td>
<td>40</td>
<td>0–50</td>
<td></td>
</tr>
<tr>
<td>Cryptorchid</td>
<td>22</td>
<td>21± 18</td>
<td>21</td>
<td>0–47</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*The 28 patients with prenatal diagnosis were excluded from this analysis
**Function distribution of the worse kidney based on DTPA or DMSA scintigraphy

Table 2. Serum creatinine (s-crea) at presentation and 6 and 12 months later in PUV patients without and with cryptorchidism.

<table>
<thead>
<tr>
<th>s-crea (µmol/L)</th>
<th>Non-cryptorchid</th>
<th>Cryptorchid</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>at presentation</td>
<td>106 87 (14–593)</td>
<td>21 100 (38–460)</td>
<td>0.131</td>
</tr>
<tr>
<td>at 6 months</td>
<td>60 45 (19–504)</td>
<td>13 90 (31–573)</td>
<td>0.006</td>
</tr>
<tr>
<td>at 12 months</td>
<td>68 46 (19–455)</td>
<td>18 52 (27–284)</td>
<td>0.524</td>
</tr>
</tbody>
</table>

URINOMAS (II)

Urinoma was detected in 17 (9%) of 196 patients. Four (4%) of 112 patients before the ultrasonography era from 1953 to 1979 and 13 (15%) of 84 patients later from 1980 to 2003 had extrarenal urinary extravasation. Abdominal distension or palpable mass in flank was registered in 9 cases with urinoma. The remaining 8 patients had an incidental finding in US (6 patients) or x-ray (2 patients). PUV was diagnosed prenatally in 5 (29%) of 17 patients with urinoma and in 22 (32%) of 69 patients without urinoma.

The escape of urine took place in three separate anatomic locations. Perirenal urinoma was observed in 9 (53%) of 17 patients, 5 on the right and 4 on the left side. Urinary ascites was found in 6 patients (35%). One of these also had extensive retroperitoneal urinoma. Urinothorax was noted in 2 patients (12%), both having fluid that had escaped into the right pleural cavity.
All patients with urinoma were noted to have bilateral dilatation of UUT. Vesicoureteral reflux was observed in 11 (7 unilaterally, 4 bilaterally) (69%) of the 16 patients with urinoma and in 51 (76%) of the 67 control cases (p=0.536). Five (56%) of the 9 patients with perirenal urinoma had VUR. Three perirenal urinomas were located ipsilaterally and two contralaterally to VUR. In one patient with perirenal urinoma, VUR was not checked (a neonate who died from severe pulmonary hypoplasia at the age of 6 days). Five (83%) of the 6 patients with urinary ascites and one patient with urinothorax also had VUR.

Values of serum creatinine measurements did not differ in patients with and without urinoma at presentation and during the first year of life (Table 3). Patients with perirenal urinoma had a median serum creatinine of 142 (range 54-204) µmol/L at presentation, and patients with urinary ascites had the same value, 142 (range 73-395) µmol/L (p=0.558). The median creatinine values at 6 months after diagnosis were 48 (range 33-150) µmol/L in patients with perirenal urinoma and 39 (range 31-230) µmol/L in patients with urinary ascites (p=0.462).

Four (25%) of the 16 patients with urinoma and 16 (23%) of the 69 patients without urinoma progressed to ESRD during childhood.

In 6 patients with perirenal urinoma (4 patients with urinary ascites, 2 boys with urinothorax), DTPA scintigraphy was done and renal split function was analysed. In patients with urinoma, split function of 51% (range 38-70%) ipsilaterally was observed. The function was lower on the side of urinoma in 2 patients and on the contralateral side in one patient. The remaining 3 patients had similar kidney function on both sides. Three of the patients with ascites had reduced kidney function on one side (0%, 9% and 33%, respectively). The patients with urinothorax had a split function distribution of 65% and 34% on the side of pleural effusion.

Bladder drainage was established postnatally in all patients after the detection of urethral obstruction. In addition, ureterocutaeostomy was performed on 13 patients. The pleural cavity was drained with needle aspiration in one patient and with a chest tube in the other patient with urinothorax. Two patients, one with urinoma and the other with ascites, underwent primary nephrectomy.
RESULTS

Table 3. Serum creatinine (s-crea) at presentation, 6 and 12 months later and nadir during the first year after diagnosis in PUV patients without and with urinoma.

<table>
<thead>
<tr>
<th>s-crea (µmol/L)</th>
<th>No urinoma</th>
<th>Urinoma</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n median (range)</td>
<td>n median (range)</td>
<td></td>
</tr>
<tr>
<td>at presentation</td>
<td>56 126 (19-593)</td>
<td>14 145 (54-431)</td>
<td>0.547</td>
</tr>
<tr>
<td>at 6 months</td>
<td>43 46 (19-573)</td>
<td>10 46 (31-230)</td>
<td>0.725</td>
</tr>
<tr>
<td>at 12 months</td>
<td>44 48 (22-455)</td>
<td>10 45 (33-154)</td>
<td>0.548</td>
</tr>
<tr>
<td>nadir value</td>
<td>49 43 (18-573)</td>
<td>11 43 (22-230)</td>
<td>0.848</td>
</tr>
</tbody>
</table>

PRIMARY VOIDING PRESSURES AND KIDNEY FUNCTION IN INFANTS (III)

Primary bladder capacity was a median of 22 (range 5-125) ml in PUV patients and 38 (range 6-129) ml in the control group (p=0.061) at a median age of 0.5 (range 0-10.2) months and 3.3 (range 1.5-9.6) months, respectively. The CBC values showed considerable variation among individuals. The measurements before and after abolition of valves did not, however, differ significantly. In addition, in patients with or without VUR the CBC values were similar (Figure 4).

Pmax det values during voiding also showed marked interindividual variation. Primary median Pmax det values of patients and controls, 112 (range 40-331) cmH₂O and 91 (range 48-191) cmH₂O, respectively, did not differ significantly (p=0.397). Pmax det levels in the primary urodynamic studies in patients before or after valve ablation, as with or without VUR, were of the same magnitude (Figure 4). Measured Pmax det values, although high, were consistent with the pressure levels in male infants with variable diagnoses in previous studies (Holmdahl et al. 1995, Sillén et al. 1996, Bachelard at al. 1998, 1999, Yeung et al. 1998, Ichino et al. 2007).

A follow-up urodynamic study after one month revealed an insignificant increase in median bladder capacity from 22 (range 5-125) ml to 23 (range 9-169) ml (p=0.278) and an insignificant decrease in median maximal voiding pressure from 112 (range 40-331) cmH₂O to 102 (range 53-300) cmH₂O (p=0.196). By contrast, one year after abolition of the valves there was a significant increase in median bladder capacity to 112 (range 40-256) ml and a significant decrease in median maximal voiding pressure to 100 (range 60-193) cmH₂O (p<0.001 and p=0.011, respectively).

No significant association was present between Pmax det and serum creatinine levels at the time of diagnosis or at the 6-month follow-up (R=-0.271, p=0.200 and R=-0.224, p=0.304, respectively). However, the patients with the highest serum
Creatinine levels had relatively low voiding pressures, whereas the patients with the highest voiding pressures had rather low serum creatinine values (Figure 5). No association existed between high voiding pressures and unilateral poor functioning kidney. Neither was there a correlation between CBC values at presentation and serum creatinine levels during the first year of life.

Again, no significant correlation was observed between bladder capacity and maximal voiding pressures in PUV patients ($R = -0.093, p = 0.665$), but a significant negative correlation was found in the control group ($R = -0.497, p = 0.031$).

Figure 4. Urodynamics in infant PUV patients around valve ablation. Cystometric bladder capacity (CBC) and maximal detrusor pressure during voiding (Pmax det). VUR-/VUR+ = patients without/with VUR.
VESICOURETERAL REFLUX (IV)

Vesicoureteral reflux was confirmed in 127 (64%) of 197 patients. VUR was bilateral in 73 patients (37%) and unilateral in 54 (27%). Unilateral reflux was on the right side in 31 patients (57%) and on the left side in 23 (43%). VUR was grade V in 116 (59%), grade IV in 47 (24%), grade III in 16 (8%), grade II in 4 (2%) and grade I in 4 (2%) ureters. Median age at presentation of PUV was 0.3 (range 0-25.5) years. Of the 99 postnatally presented patients, the diagnosis was made at a younger age in those with VUR than without VUR (median ages 0.3 (range 0-14.6) years and 2.9 (range 0-25.5) years, respectively, p<0.001). Reflux was registered in 17 (61%) of the 28 patients with an antenatal diagnosis of PUV.

At the time of diagnosis, refluxing patients had significantly higher serum creatinine levels than patients without VUR (Table 4). This was a conspicuous finding particularly in bilateral VUR, in which the significance persisted at the 6- and 12-month follow-ups. In addition, ESRD developed significantly more often in patients with bilateral reflux.

Primary scintigraphy revealed also a very poor kidney on the refluxing side, with split function of less than 10% in 22 (30%) of the 73 patients investigated. Of the 35 patients without VUR, 2 (6%, p= 0.006) had such poorly functioning kidneys in scintigraphy. The median split function of worse kidney was significantly lower not only in unilateral VUR cases but also in bilateral cases than in patients without
VUR (Table 4). In unilateral cases, the median split function on the refluxing side was 31% (range 0-58) and on the contralateral side 69% (range 42-100) (p<0.001).

In the early series, 11 refluxing ureters in 10 patients were operated on before or at the time of valve ablation. In 4 patients, nephrectomy was done elsewhere prior to admission to our hospital and valve ablation. In another 5 patients unilateral, and in one patient bilateral ureteral reimplantation was performed.

Follow-up data were available for 141 refluxing ureters, while 49 ureters were lost to follow-up or documentation was inadequate. In 88 ureters (62%), VUR resolved spontaneously, in 29 ureters (21%) following antireflux surgery and in 24 ureters (17%) after nephrectomy.

Over the long study period, VUR in PUV patients has been subjected to different treatment options. Ureterovesical surgery was done almost exclusively early in the series or elsewhere before referral to our hospital. Nephrectomies were performed in cases with non-functioning or only marginally functioning kidneys where massive VUR usually persisted. Unilateral nephrectomy in patients with ipsilateral massive reflux and non-functioning kidney was performed on 35 patients (18%), 18 on the right side and 17 on the left. VUR had resolved, however, in 11 of the 35 cases before nephrectomy. Of patients with unilateral and bilateral VUR, nephrectomy was performed on 20 (37%) and 15 (21%) cases, respectively. Also 3 (4%) of the 70 patients without VUR were submitted to nephrectomy.

Resolution of VUR was observed in a median of 1.28 (range 0.04-15.16) years after release of urethral obstruction in those ureterorenal units not subjected to reimplantation or nephrectomy. The elapsed time in 24 patients with unilateral reflux was 0.71 (range 0.04-7.93) years and in 64 patients with bilateral reflux 1.36 (range 0.04-15.16) years (p=0.049). No correlation existed between kidney split function and resolution of VUR (r=0.19, p=0.37). However, resolution was noted to be faster in grade I-III than in grade IV-V reflux, with a median of 0.68 (range 0.14-15.16) years and 1.47 (range 0.04-15.16) years, respectively (p=0.054).

In the 68 patients born between 1980 and 2003 and primarily treated in our hospital, 20 had unilateral and 19 bilateral VUR. Of these 58 refluxing ureters, 31% resolved during the first and 19% during the second year after release of urethral obstruction (Table 5).
RESULTS

Table 4. Serum creatinine levels (mean± SD, median (range)) at presentation and at 6 and 12 months after resection of PUV in patients without VUR (Group 1), with unilateral VUR (Group 2) and with bilateral VUR (Group 3).

<table>
<thead>
<tr>
<th></th>
<th>Group 1 mean±SD (range)</th>
<th>Group 2 mean±SD (range)</th>
<th>Group 3 mean±SD (range)</th>
<th>p-value &lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-crea (µmol/L) at presentation</td>
<td>45 87± 67 66 (19–374)</td>
<td>39 144± 125 97 (21–433)</td>
<td>47 155± 122 130 (14–593)</td>
<td>Gr 1 vs. Gr 2 and Gr3</td>
</tr>
<tr>
<td>S-crea (µmol/L) at 6 months postoperation</td>
<td>25 50± 43 43 (19–229)</td>
<td>23 83± 114 43 (22–504)</td>
<td>26 116± 128 58 (20–573)</td>
<td>Gr 1 vs. Gr 3</td>
</tr>
<tr>
<td>S-crea (µmol/L) at 12 months postoperation</td>
<td>30 50± 46 43 (19–284)</td>
<td>28 79± 96 46 (22–455)</td>
<td>29 90± 66 57 (28–292)</td>
<td>Gr 1 vs. Gr 3</td>
</tr>
<tr>
<td>Split renal function (%) on worse kidney</td>
<td>35 40± 12 45 (0–50)</td>
<td>34 26± 19 31 (0–49)</td>
<td>39 25± 17 29 (0–50)</td>
<td>Gr 1 vs. Gr 2 and Gr3</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>Spontaneous resolution of VUR n (%)</th>
<th>Cumulative spontaneous resolution %</th>
<th>Nephrectomy n (%)</th>
<th>Antireflux surgery n (%)</th>
<th>Persisting VUR at last control n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>18 (31.0)</td>
<td>31</td>
<td>1 (1.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1-2</td>
<td>11 (19.0)</td>
<td>50</td>
<td>5 (8.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-3</td>
<td>5 (8.6)</td>
<td>59</td>
<td>1 (1.7)</td>
<td>0</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td>3-4</td>
<td>1 (1.7)</td>
<td>60</td>
<td>0</td>
<td>1 (1.7)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>4-5</td>
<td>1 (1.7)</td>
<td>62</td>
<td>0</td>
<td>1* (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>5-6</td>
<td>1 (1.7)</td>
<td>64</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6-7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7-8</td>
<td>0</td>
<td>2 (3.4)</td>
<td>0</td>
<td>0</td>
<td>3 (5.2)</td>
</tr>
<tr>
<td>8+</td>
<td>2 (3.4)</td>
<td>67</td>
<td>0</td>
<td>0</td>
<td>3 (5.2)</td>
</tr>
</tbody>
</table>

*Deflux® injection to ureteric orifice
LONG-TERM RISK OF END-STAGE RENAL DISEASE (V)

Of the 193 PUV patients, 44 (22.8%) progressed to ESRD at the median follow-up age of 31 (range 6-69) years. Thirty (68%) of these 44 patients with ESRD had progression before the age of 17 years and 14 patients (32%) later. Renal failure was the cause of death in 9 patients (4.6%), in 2 under the age of one year, in 3 at the age of 4 years and in 4 between the ages of 12 and 17 years. The highest age at onset of ESRD was 34 years, while 59 of the patients were older than that but without ESRD at the time of evaluation. The probability of developing ESRD during the life-time according to Kaplan-Meier analysis was 28.5% (SE 3.8%, Figure 6).

The cumulative risk for ESRD was 16.7% (SE 3.4%) before the age of 27 years in the early series of 121 patients born between 1953 and 1981 before the prenatal US era and 36.6% (SE 7.7%) in the later series of 72 patients born between 1982 and 2003 (Figure 6). In the Kaplan-Meier survival plot, the probability of ESRD was 54.8% (SE 14.1%) in patients with an antenatal diagnosis, 31.9% (SE 14.1%) in patients with early neonatal problems and 22.1% (SE 10.0%) in patients with infection at presentation (Figure 7). In the series from the US era, 28 patients had an antenatal diagnosis and 44 a postnatal diagnosis. In this late cohort, 10 patients (36%) in the antenatal group and 7 patients (14%) in the postnatal group developed ESRD (p=0.047).

Primary serum creatinine values were significantly higher in the 28 patients contracting end-stage renal failure than in the 100 non-ESRD-developing patients, with median values of 173 (range 46-593) µmol/L and 70 (range 14-460) µmol/L, respectively (p < 0.001). Also the lowest creatinine values during the first postoperative year were significantly higher in the 24 patients progressing to ESRD than in the 74 non-ESRD-developing ones (median 134 (range 45-573) µmol/L and 38 µmol/L (range 14-97) µmol/L, respectively, p<0.001). All patients with nadir creatinine above 97 µmol/L during the first year after diagnosis developed ESRD, whereas no patient with serum creatinine less than 45 µmol/L progressed to ESRD. In addition nadir creatinine during the first postoperative year was observed to be associated with the speed of progression of ESRD.

Those patients who had pneumothorax or bilateral VUR at presentation or recurrent UTIs after abolition of valves had significantly increased risk for ESRD at follow-up (Table 6). However, urinoma or unilateral VUR at the time of diagnosis or delayed urinary continence did not show such a risk for ESRD (Table 6, Figure 8).
RESULTS


Figure 7. Kaplan-Meier analysis. Renal survival of patients with different modes of presentation.
Figure 8. Kaplan-Meier analysis. Presence of VUR at diagnosis and renal survival.

Table 6. Characteristics and their relation to ESRD in PUV patients.

<table>
<thead>
<tr>
<th></th>
<th>All (n=193)</th>
<th>No ESRD (n=149)</th>
<th>ESRD (n=44)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinoma</td>
<td>17/193 (8.8%)</td>
<td>14/149 (9.4%)</td>
<td>3/44 (6.8%)</td>
<td>0.767</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>10/193 (5.2%)</td>
<td>3/149 (2.0%)</td>
<td>7/44 (15.9%)</td>
<td>0.002</td>
</tr>
<tr>
<td>VUR</td>
<td>123/192 (64.1%)</td>
<td>88/149 (59.1%)</td>
<td>35/43 (81.4%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Bilateral</td>
<td>72/192 (37.5%)</td>
<td>45/149 (30.2%)</td>
<td>27/43 (62.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unilateral</td>
<td>51/192 (26.6%)</td>
<td>43/149 (28.9%)</td>
<td>8/43 (18.6%)</td>
<td>0.240</td>
</tr>
<tr>
<td>Recurrent UTIs postoperation</td>
<td>35/193 (18.1%)</td>
<td>19/149 (12.8%)</td>
<td>16/44 (36.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enuresis (after age of 5 years)</td>
<td>70/193 (36.3%)</td>
<td>55/149 (36.9%)</td>
<td>15/44 (34.1%)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>
The incidence of cryptorchidism in our patients was 16%. It has previously been reported to be 12% among boys with PUV (Krueger et al. 1980b). In another report, 17% undescended testes were originally found in conjunction with PUV (Barker et al. 1993). In this latter series, patients with prune belly and Noonan syndromes were, however, included, and when these syndromes were removed the figure dropped to 12% (Barker et al. 1993). In a recent unselected Finnish male population, the incidence of cryptorchidism was 1.0% at the ages of both 3 and 18 months (Boisen et al. 2004). In our PUV patients, the risk rate of cryptorchidism was therefore 16-fold higher. UDT occurred bilaterally in 29% of cases. This exceeds the 20% reported in an unselected cryptorchid population and in one of the earlier studies with PUV (Boisen et al. 2004, Barker et al. 1993), but is somewhat less than the 42% found in the other PUV study (Krueger et al. 1980b).

Our patients with cryptorchidism had a more severe form of PUV. The diagnosis of PUV was made earlier and kidney function was worse in the cryptorchid group. In the earlier reports, undescended testes were also more common in patients with a neonatal diagnosis and obviously in those with more severe PUV (Krueger et al. 1980b, Barker et al. 1993). This finding makes it appealing to propose that urethral obstruction per se constitutes the failure in testicular migration. Earlier, in foetuses with PUV, the amount of foetal germ cells has been noted to be reduced (Orvis et al. 1988). Testicular endocrinopathies have not been reported in PUV patients after puberty (Puri et al. 2002). In this retrospective study, hormonal measurements were not done. Thus, definitive conclusions about whether diminished renal function and adverse effects on hormonal balance or mechanical reasons are responsible for PUV cannot be drawn.

The incidence of inguinal hernias in our patients (11%) was higher than in the general child population (1.5%) (Yücesan et al. 1993). The 7-fold incidence may have the same aetiological background as cryptorchidism in PUV patients. Inguinal hernias were found to be associated with severe forms of PUV, but not as strongly as cryptorchidism.

The incidence of urinomas among PUV patients in our series was 9%. It is just slightly higher than the previously reported 1-8.5% (Greenfield et al. 1982, Rittenberg et al. 1988, Patil et al. 2003). In the early series in our study before the time of ultrasonography, only 4% of the patients were found to have urinoma. After US became routine in clinical use, 15% of the PUV patients were detected to have urinoma. The latter figure probably reflects the advantage of US studies in diagnostics and indicates the true incidence at the moment. In a recent US study, 2
of 8 patients were found to have a perirenal fluid collection (Donnelly et al. 1997). Urinoma, previously regarded as a rare complication of PUV, has proven to be more common. In the present study, reflux was seen in 69% of the patients with perirenal urinoma and in 83% of the patients with urinary ascites, and even in one of 2 patients with urinothorax. In a previous report, VUR has been concluded to be a companion of perirenal urinoma, but not of urinary ascites (Patil et al. 2003). This argument is contrary to our findings.

Urinomas have been proposed to protect overall renal function in many reports (Kay et al. 1980, Rittenberg et al. 1988, Fernbach et al. 1990, Donnelly et al. 1997, Lee et al. 2005). In recent studies, this statement has been questioned (Patil et al. 2003, Kleppe et al. 2006). Renal function has actually even been described as impaired on the side of the perirenal urinoma (Patil et al. 2003). Our findings did not show any particular benefit or harm from urinomas to renal function. Two of our patients had somewhat lower function on the side of the urinoma and one on the contralateral side. Kidney function of patients with urinomas and controls did not differ as a rule. Liability to more severe obstruction cannot, however, be excluded.

After primary drainage, 3 patients were managed with valve ablation only in our series, 13 patients had ureterocutaneostomy and both patients with urinothorax had drainage of the pleural cavity. Whether all procedures were actually necessary cannot be definitively ascertained from this retrospective material. In a recent report, bladder drainage and observation were preferred, and aspiration was deemed to be indicated only in symptomatic urinomas (Patil et al. 2003). Only in 2 of 18 cases was nephrostomy or ureterostomy performed in that study.

In our series, only symptomatic cases of urinomas were detected and treated with temporary diversion. Urinary diversion in these patients was seen to augment effective stabilization of the overall condition. Currently, however, more urinary extravasations may be observed and only unsatisfactory clinical course after initial bladder drainage may demand additional interventions, as was concluded by Patil et al. (2003).

In PUV patients, dysplastic changes in kidneys have been proposed to be caused by abnormal development of ureteric bud or bladder outlet obstruction itself (Gonzalez et al. 1990, Farrugia et al. 2007). In experimental models, severe bladder outlet obstruction has been observed to lead to renal dysplasia (Gonzalez et al. 1990, Farrugia et al. 2007). Infravesical obstruction in a recent experimental foetal ovine study caused an increase in the duration and frequency of elevated voiding pressures (Farrugia et al. 2007). Foetal kidney development was disturbed by altered bladder dynamics in that study. Also in infant PUV patients marked detrusor hypercontractility together with high voiding pressures have been observed (Holmdahl et al. 1995). The high voiding pressures found in our study
are consistent with that observation. Similar high voiding pressures, however, were detected in our control group of boys with previous UTI as well as in healthy male infants with UTI and reflux in earlier reports (Sillén et al. 1996, Bachelard et al. 1998, 1999, Yeung et al. 1998, Ichino et al. 2007). The long narrow infant male urethra and dyscoordination between the bladder and sphincter are assumed to cause these high voiding pressures (Sillén and Hjälmås 2004).

We could confirm a decline in voiding pressures after valve ablation, but a significant change was not noted until one year later. A gradual decrease in voiding pressures has been reported also among other male infant groups (Holmdahl et al. 1995, Sillén et al. 1996, Ichino et al. 2007). The somewhat higher voiding pressures in our PUV patients relative to controls may, in addition to obstruction by valves, also result from the slightly younger age of the PUV patients. In addition, there was significant interindividual variation between voiding pressures in our study, as in other studies with infants (Sillén et al. 1996, Bachelard et al. 1998, 1999).

We were unable to detect a relation between Pmax det and CBC and serum creatinine levels at the time of diagnosis or during the year thereafter. This does not, however, exclude the possible prenatal participation in voiding pressures. Moreover, Pmax det may not be the most accurate indicator of the pressure effects in UUT. The study design did not allow us to measure the duration and frequency of high intravesical pressure periods, which have been regarded as essential for adverse effects on the foetal kidney (Farrugia et al. 2007). For this type of analysis, a naturally filling cystometry is obviously required since hypercontractile bladders of PUV patients have been shown to become stable during sleep (Holmdahl et al. 1997). Noteworthy is that there was a peculiar non-significant trend towards higher voiding pressures in patients with better kidney function.

In our study, the maximal voiding pressures did not differ in patients with and without VUR. A similar observation has previously been reported (Holmdahl et al. 1995). In our study, also the measured bladder volume did not differ in patients with and without VUR. In refluxing patients, measurement of bladder volume without videocystometry may, however, be imprecise.

In our study, 64% of all PUV patients had vesicoureteral reflux. This is in accordance with earlier reports, with VUR occurring in 26-72% of boys with PUV (Dinneen and Duffy 1996). VUR was bilateral in 37% and unilateral in 27% of cases in the present series, which is in line with previous albeit smaller series, with bilateral VUR ranging from 32% to 37% and unilateral VUR from 25% to 35% (Johnston 1979, Priti et al. 2004). VUR especially bilaterally in PUV patients has been observed to accompany impaired overall kidney function (Johnston 1979, Tejani et al. 1986, Parkhouse et al. 1988, Denes et al. 1997, Oliveira et al. 2002). In our study, the serum creatinine levels at presentation were significantly higher in VUR patients than in non-VUR patients. Serum creatinine levels also remained
high during the first year in patients with bilateral VUR and to a lesser degree in those with unilateral VUR. These values were still higher 5-7 years after ablation of valves in patients with VUR. The great majority of patients who progressed to ESRD during childhood had VUR, mostly bilaterally. The postnatally detected refluxing patients were also younger at the time of diagnosis than those without VUR. Younger age at presentation as well as impaired kidney function before and after valve ablation have been shown to indicate late poor renal function (Scott 1985, Drozdz et al. 1998, Lopez Pereira et al. 2003).

Previously, a high incidence of non-functioning kidneys has been noted in cases with ipsilateral VUR (Hoover and Duckett 1982, Greenfield et al. 1983, Donnelly et al. 1997). In these patients, non-functioning kidneys and refluxing units have been reported to occur more commonly on the left side. A pop-off mechanism has been speculated to protect the contralateral side (Hoover and Duckett 1982, Greenfield et al. 1983, Donnelly et al. 1997, Oliveira et al. 2002). The concept that unilateral reflux protects the contralateral kidney is not, however, supported by all authors (Cuckow et al. 1997, Drozdz et al. 1998, Lopez Pereira et al. 2003). In our study, the contralateral split function was significantly higher than that on the VUR side. The overall kidney function did not, however, differ or it was only slightly reduced in patients with unilateral VUR relative to those without VUR. These findings thus do not lend support for a protective pop-off effect. In patients with VUR, we did not detect left-side dominance in non-functioning kidneys. Of the 35 removed non-functioning kidneys, 18 were on the right and 17 on the left side.

After abolition of valves, VUR is known to resolve in many patients. Johnston reported resolution of reflux in 30 (46%) of 65 ureters in 44 patients during a follow-up lasting from 2 weeks to 13 months (Johnston 1979). More recently, VUR has been reported to resolve in 27-40% of refluxing ureters after a follow-up of 1-21 years (Scott 1985, Lal et al. 1998b, Farhat et al. 2000), and in 64% of patients with PUV during a mean follow-up of 6.3 years after treatment of valves (Connor and Burbige 1990). In our study, VUR was observed to resolve in 62% of ureters in a median of 1.28 (range 0.04-15.16) years after valve resection. In unilateral cases, VUR subsided significantly sooner than in bilateral cases.

Vesicoureteral reflux in PUV patients is presumably secondary to infravesical obstruction. Thus, after ablation of valves resolution of VUR is expected. The rate of spontaneous resolution of VUR was not affected by the kidney split function in the present study, and in 11 ureters VUR subsided even on the side of the non-functioning kidney. Resolution of reflux in a non-functioning unit has been shown before (Kim et al. 1997). Low-grade reflux, however, showed a trend towards faster resolution in our series. A weakness of our retrospective analysis is that radiographs and radionuclide cystographies after valve ablation were not done following a consistent regimen but after individualized timetables, particularly in the early series.
DISCUSSION

Auxiliary operative procedures were performed on numerous patients with VUR. Antireflux surgery was carried out for 21% and nephrectomy for 17% of refluxing ureters. In many early cases, indications for these surgical procedures could not be defined accurately and also the operative techniques had varied over time. There is evidence that reimplantations are liable to hazards, with complication rates of 45-67% described in PUV patients (Atwell 1983, Tejani et al. 1986). However, ureteral surgery has its proponents, although the results do not necessarily reach expectations at present (El-Sherbiny et al. 2002). Practically all reimplantations in our study material were performed in the early series or elsewhere before referral to our hospital. Since antireflux surgery was utilized mostly rather soon after abolition of valves, it may be justified to conclude that some of the procedures might not have been necessary.

We also analysed separately the spontaneous resolution rate of VUR after ablation of PUV in the late series (39 patients) with more standardized x-ray and isotope studies. In that cohort, 57% had VUR, and it subsided in 31% and 50% of the refluxing ureters after a follow-up of one and two years, respectively. In 67% of the units, VUR resolved by 8 years. We have very seldom found indications for ureteral reimplantation.

In patients with persistent VUR and recurrent UTIs, or marginally functioning kidneys after valve resection, we start clean intermittent catheterizations (CIC), or perform ring-type temporary supravesical diversions. In these severely ill patients, also others have suggested CIC and vesicostomy or ureterocutaneostomy to control infection and stabilize the overall situation (Denes et al. 1997, Farhat et al. 2000, Liard et al. 2000, Haecker et al. 2002, Ghanem and Nijman 2005). In the present series, the few older patients with persistent VUR did not have recurrent UTIs or compromised renal function, and successive cystograms were not considered justified.

A non-functioning kidney with VUR is thought to be susceptible to disturbances of bladder function and UTIs. In the present study, we were not able to test this concept, but in many patients bouts of pyelonephritis were seen as a contributory factor when considering indications for nephrectomy. The incidence of unilateral nephrectomies in our series was 18%, which is in line with the previously reported 17-19% (Atwell 1983, Cuckow et al. 1997, Holmdahl and Sillén 2005). Nephrectomy in these situations can be deemed justified.

To our knowledge, this is the largest systematic study with the longest follow-up to assess the progression of ESRD in patients with PUV. The onset of ESRD was defined as the start of dialysis or the date of death to chronic uremia. Nearly one-fourth (22.8%) of these 193 patients progressed to ESRD during a median follow-up of 31 years. Of the ESRD patients, about two-thirds (68%) had the progression as a child before the age of 17 years and one-third (32%) as an adult. Early diagnosis, high primary serum creatinine values, pneumothorax, bilateral
VUR at presentation and recurrent UTIs after abolition of the valves were related to poor prognosis. The calculated life-time risk for ESRD was 28.5%. However, in the early series among those born before 1982 in the pre-sonography era, the risk for ESRD was only 16.8% before the age of 27 years. In turn, among those born later in the post-sonography era, the risk for developing ESRD before the age of 27 years was 36.6%. Accordingly, also true life-time risk presumably will rise. A better outcome in the early series was obvious, and a likely explanation is that many critically ill patients died without referral to our hospital. In addition, in the later series there may be burden of severely ill patients since ours is the only hospital performing renal transplantations for children in our country.

The most common ages for developing ESRD in PUV patients have been concluded to be the first year of life and adolescence. (Smith et al. 1996) The follow-up in that study, however, included only children. We could verify that the progression was rather steady up to the age of 34 years, and only a moderate slope was seen in the progression during the first year of life and in adolescence. A recent study from Sweden disclosed that 32% of their 19 adult patients developed uraemia, the oldest at the age of 37 years (Holmdahl and Sillén 2005). The oldest patient progressing to ESRD in our series was 34 years. Since 59 of our patients had achieved ages higher than that, it may be justified to predict that progression to chronic renal failure diminishes with age.

Maternal US screening offers a notable advantage in diagnosing posterior urethral valves (Roth et al. 2001). With the advent of prenatal diagnosis, it was anticipated that the greatest benefit would be for infants with PUV by facilitating early postnatal decompression, shortening the duration of obstruction and minimizing the risks of infective renal damage (Thomas 2010). Prenatal recognition and early management of asymptomatic patients have been shown to improve final outcome in some reports (Kousidis et al. 2008, Thomas 2010). However, some studies have failed to demonstrate that outcome is better with prenatal presentation (Yohannes and Hanna 2002, Hodges et al. 2009). We could show higher risk for ESRD in patients with an antenatal diagnosis. A likely explanation for this finding is that the most severe cases were more often detected prenatally. Our observation is in line with earlier studies with a shorter follow-up (Reinberg et al. 1992, Jee et al. 1993). The rather liberal policy to terminate pregnancies with obstructive uropathies in some countries can impact the renal survival figures. In the present study, there was no selection in this respect since the termination of pregnancy due to PUV is very rare in our country. Most antenatal cases in this work were detected at screening during gestation weeks 18-20.

In our study with a very long follow-up, we could confirm that serum creatinine values at presentation and during the following year have a correlation with prognosis. This observation is consistent with earlier studies with shorter follow-ups (Denes et al. 1997, Drozdz et al. 1998, Oliveira et al. 2002, DeFoor et al. 2008).
Furthermore, we were able to verify that primary serum creatinine values have an impact on the speed of progression to ESRD. Rather low serum creatinine values at presentation in our study did not exclude later ESRD, a finding in agreement with some earlier reports with shorter follow-ups (Roth et al. 2001, Kousidis et al. 2008, Denes et al. 1997).

Respiratory distress and pulmonary hypoplasia are known malicious associations in neonates with severe PUV (Yohannes and Hanna 2002, Hodges et al. 2009). In this study, pneumothorax was used as the indicator of respiratory symptoms because it was recorded well throughout the series. Pneumothorax was seen to accompany poor kidney outcome. Ten of the patients had pneumothorax at presentation, and more than half of them progressed to ESRD.

In our follow-up study, bilateral VUR constituted a poor prognostic factor for overall renal function. However, unilateral VUR and urinomas had no impact on renal prognosis. VUR has been considered to be a risk for renal malfunction in some (Parkhouse et al. 1988, Roth et al. 2001, Oliveira et al. 2002, Ghanem et al. 2004) but not all reports (DeFoor et al. 2008, Kousidis et al. 2008). Kidneys with VUR was observed to have reduced function in PUV patients primarily. By contrast, urinomas and unilateral VUR at presentation have been suggested to preserve renal function through a pop-off mechanism (Claahsen-van der Grinten et al. 2002, Oliveira et al. 2002, Wells 2010). Our experience does not provide support for this pop-off theory, in accord with some earlier reports (Patil et al. 2003, Kleppe et al. 2006).

Dysfunction of the lower urinary tract is known to be common in PUV patients, and prompt management has been deemed crucial (Glassberg 2001). Correct treatment may also reduce infection rates, although this aspect has not been thoroughly clarified. Urinary tract dysfunction and urinary incontinence have been suggested to predict poor renal function in PUV patients in some (Parkhouse et al. 1988, Lopez Pereira et al. 2002, Holmdahl and Sillén 2005, DeFoor et al. 2008) but not all reports (Kousidis et al. 2008, Sarhan et al. 2008). In the present study, recurrent UTIs were associated with poor outcome and impairment of renal function. This finding is in agreement with some earlier observations (Denes et al. 1997, Roth et al. 2001, Holmdahl and Sillén 2005). In our study, urinary incontinence after the age of five years was common (36%), but was not found to indicate later renal failure. In the early series, incontinence or its quality was not, however, always registered, and thus, potential reporting bias cannot be excluded.
Early features and late follow-up of patients with PUV during the 51-year period (1953-2003) were assessed in this study. Patient characteristics, presentation, associated anomalies, surgical management, early and late renal function and causes of death were sought. In addition, a cohort of infant patients from 1994 to 2007 was analysed for early bladder function.

The main conclusions of the study are as follows:

1. Posterior urethral valves often lead to ESRD with age. In the mid-thirties, the risk subsided in this study. Early presentation, poor primary renal function, pneumothorax perinatally as well as VUR bilaterally and recurrent UTIs during childhood carry a risk for deterioration of renal function and ESRD. These risk factors should be recognized, proper management initiated and follow-up extended throughout childhood to adulthood.

2. The incidence of VUR in PUV patients at the time of presentation is high, 64% in the present study. Bilateral VUR is often accompanied by reduced overall kidney function. The kidneys of refluxing units seem to have worse primary function than the contralateral kidneys. Spontaneous resolution of VUR was observed to occur at a median of 1.28 years after abolition of valves, more rapidly in unilateral than bilateral cases. Antireflux surgery is most often not justified.

3. The incidence of cryptorchidism is 16-fold higher and the incidence of inguinal hernia 7-fold higher in PUV patients than in the normal population. Cryptorchidism and inguinal hernias are more common in patients with severe PUV. The underlying pathophysiological mechanisms remain unclear.

4. High voiding pressures were seen in infants around the ablation of valves. However, maximal voiding pressures were similar in an institutional control group and in male infant groups with different aetiologies according to previous reports. In our study, no correlation between high voiding pressures and poor primary kidney function was observed. The voiding pressures were registered to decrease slowly during the months following the release of the valvular obstruction.
CONCLUSIONS

5. The current incidence of urinomas in PUV patients is presumably close to 15%. The renal function is similar in PUV patients with or without urinoma as well as in cases with perirenal urinoma and urine ascites. The abolition of valves in asymptomatic cases is probably the only justified procedure in PUV patients with urinoma.
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