Posterior Urethral Valves

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35.1 Anatomy

The male urethra can be divided into four segments:

- Prostatic urethra.
  - From the bladder neck to the site of the urogenital diaphragm.
- Membranous urethra.
  - Urogenital diaphragm.
- Bulbar urethra.
  - From the distal margin of the urogenital diaphragm to the penoscrotal junction.
- Penile urethra.
  - Urethra that traverses the penile shaft including the glans.

Posterior urethral valves (PUV) results from an anomalous insertion of the mesonephric duct into the urogenital sinus, preventing normal migration of these ducts and their anterior fusion forming the abnormal ridges in the membranous urethra.

35.2 Classification

Traditionally, three types of posterior urethral valves have been described as Young's Classification[1] (Table 35.1).

[1] Hugh Hampton Young—Father of American urology, described classification in 1919.

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Table 35.1 Young's[2] classification of posterior urethral valves

Type	Description	Result
I (~95%)	Bicuspid valve from posterior edge of the verumontanum extending distally and anteriorly and fusing in the midline	Obstructive
II	Prominent longitudinal folds extending from verumontanum toward the bladder neck	Nonobstructive
III (5–10%)	Circumferential ring distal to the verumontanum at the level of the membranous urethra	Obstructive

- **Congenital Obstructing Posterior Urethral Membrane (COPUM)** is a newer concept whereby the un-instrumented urethra looks more like a circumferential obstructing membrane with a small central or eccentric opening, which following catheterization or instrumentation reverts to the classical "valve" appearance.

35.3 Epidemiology

A recent national audit (BAPS-CASS) from the UK and Ireland identified the incidence of PUV to be:

- 1 in 3800 male births. 3
- 50% of patients with PUV were diagnosed antenatally.
  - 42% within the first year of life and 23% were late diagnosis.

35.4 Pathophysiology

The posterior urethral obstruction represents a mechanical obstruction leading to secondary pathological changes to the upper tracts. Severity depends on:

- Degree of obstruction.
- Timing of the obstruction.
- Genotypic factors responsible for ureteral bud anomalies and nephrogenesis predisposing to **end-stage renal disease (ESRD).**

Experimentally induced fetal bladder outflow obstruction has established the following effects:

- Bladder outlet obstruction (BOO).
  - Causes smooth muscle hypertrophy, hyperplasia of fibroblasts and myoblasts.
  - Due to upregulation of Hypoxia-Inducible factors (HIFs) and ↑expression of profibrotic cytokines which mediates the hypoxic response and ↑in the deposition of type III collagen extracellular matrix in the bladder wall.
  - Progressive stretch injury along with the hypoxia alters the detrusor blood flow resulting in muscular ischemia.
  - Leads to a shift to anaerobic metabolism causing irreversible damage to the nerves of the bladder wall.

This pathological process translates clinically into the following:

- High voiding pressure due to the initial hypertrophy. In early stages, the bladder is able to empty completely.
- ↓ bladder capacity and ↓ compliance caused by the remodeling of the bladder wall.
- Decompensation occurs where the compliance and contractility of the bladder are affected.
  - Leading to incomplete bladder emptying and rise in post-void residual (PVR) urine volume.
  - ↑ intravesical storage pressure.
- Upper tract change.
  - Ureteric dilation, ↓ glomerular filtration rate (GFR), ↑ intra-pelvic pressure causing tubular injury and renal parenchymal fibrosis.

35.4.1 Genetics

Angiotensin-converting enzyme (ACE) gene has been found to play an important role in ureteric bud development and nephrogenesis. During nephrogenesis ACE gene dysfunction can lead to ESRD.

Strong links between ACE (DD genotype) gene and progression to ESRD in patients with obstructive uropathies have been established.

35.5 Clinical Features

- Antenatal diagnosis.
  - Maternal US performed between 16 and 20 weeks gestation.
    - Dilated posterior urethra (Keyhole sign), hydronephrosis and hydroureter.
    - Oligohydramnios (sometimes) due to cystic or echogenic kidneys suggestive of renal dysplasia.
    - Presence of oligohydramnios before 24 weeks of gestation suggests poor prognosis. Oligo or anhydramnios often leads to pulmonary hypoplasia and Potters syndrome.[2]

Apart from PUV, differential diagnosis includes prune-belly syndrome, bilateral vesicoureteral reflux, and urethral atresia.

- Postnatal.
  - Poor stream ± palpable bladder.
  - UTI.
  - Renal failure with poor somatic growth and lethargy.
  - Diurnal incontinence and/or nocturnal enuresis.

[2] Edith Potter (1901–1993) described 20 cases in 1946. Chief of Pathology at the Chicago Lying In Hospital.

35.5.1 Investigations

- Ultrasound.
  - Used to confirm and assess the severity of the hydronephrosis and identify a perinephric urinoma, thickening of the bladder wall or urinary ascites.
- **MCUG** is considered the gold standard for the diagnosis of PUV (Fig. 35.1). Features include:
  - Dilated and elongated posterior urethra with a ratio of 5:1 to the anterior urethra.
  - Prominent bladder neck, particularly posterior lip.
  - Partial filling of anterior urethra.
  - Posterior urethral bulging forward over the bulbous urethra.
  - Vesico-ureteric reflux in 40–60% of cases (unilateral in two-third of cases).
  - Valve leaflet lucencies (occasional).
- Radionuclide studies.
  - Can be used to assess baseline differential renal function and degree of renal dysplasia.

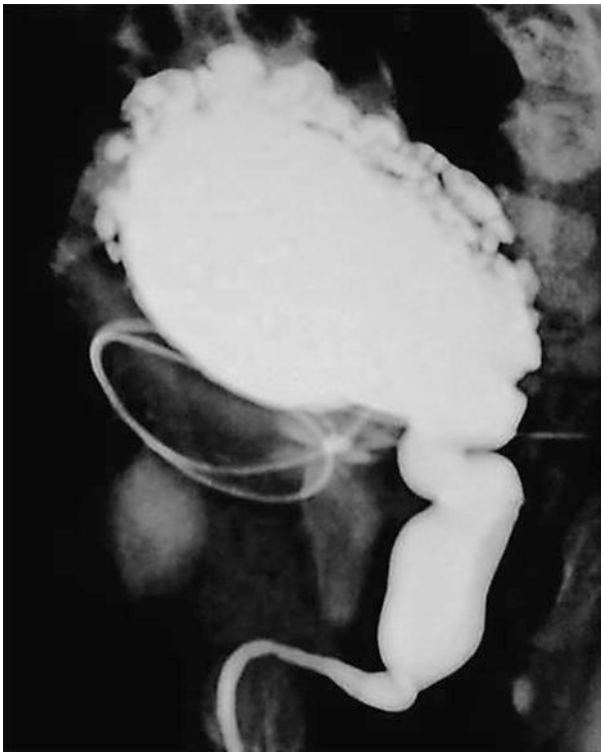

Fig. 35.1 MCUG showing posterior urethral valves with trabeculated bladder with pseudo-diverticuli

35.6 Management

- Initial management

Most neonates with posterior urethral obstruction will have a degree of electrolyte imbalance and metabolic acidosis. Initial resuscitation with intravenous hydration and electrolyte replacement should be commenced. Prophylactic antibiotics are started after sending blood and urine samples for testing and cultures.

- Bladder drainage

Temporary drainage of the bladder can be achieved by a transurethral feeding tube as balloon catheters can cause more bladder spasms, obstruct ureteric orifices leading to increased upper tract dilatation and poor emptying of ureters.

At times transurethral catheterization fails due to coiling of catheter/ feeding tube in the dilated posterior urethra and raised bladder neck. In such cases, a **suprapubic catheter** should be inserted to drain the bladder.

In case of premature neonates or poor general condition, bladder drainage is required for prolonged period. In such cases, bladder can be drained either through suprapubic catheter (SPC) or a **vesicostomy**.

- Valve Ablation

After stabilization of the neonate's general condition, **endoscopic transurethral ablation** is the treatment of choice. An endoscopic resectoscope or Bugbee™ electrode can be used to incise the obstructing membrane at the 5, 7, and/or 12 O'clock positions. Nd YAG laser has also been used to ablate PUV.

Repeat Cystoscopy and MCUG are usually performed after 4–6 weeks to confirm satisfactory valve disruption. Circumcision should be offered at the time of cystoscopy to reduce the risk of future UTI.

Complications of valve fulguration include incomplete ablation and urethral stricture. Urethral stricture (5%) can also result from using a bigger resectoscope compare to the size of the urethra. Residual valves are usually seen when ablation is performed using Bugbee™ electrodes.

If ablation is not feasible (small infant or lack of smaller scopes), urinary diversion should be considered. This may include vesicostomy, ureterostomy, or pyelostomy.

- Vesicostomy

The dome of the bladder bought to the skin midway between the umbilicus and the symphysis pubis. This allows drainage but also cycles urine to the bladder and maintains volume. It may be closed once renal function has stabilized, upper tracts have diminished, and the child is large enough for a valve ablation. Valve ablation

should be performed at the time of vesicostomy closure to avoid urethral stricture developing if ablation is performed in a "dry" urethra.

- Upper tract diversion

Higher levels of drainage include the **bilateral ureterostomy or pyelostomy**. Long-term studies have shown that there is no reduction in the incidence of renal failure—which is more likely to be due to intrinsic renal dysplasia. These diversion procedures also result in a small capacity bladder. Therefore, consider only when a vesicostomy is not providing adequate drainage due to poor drainage across VUJ (hypertrophic bladder causing functional obstruction) or in the presence of pyonephrosis.

- Bladder Management

Improving bladder emptying to ↓intravesical storage pressure and take pressure off the upper tracts is crucial in the management of PUV. This can be achieved by the following:

Behavioral modifications:

- Adequate fluid intake.
- Recognizing urge sensation.
- Avoid urine holding maneuvres.
- Double voiding.
- Adequate treatment of constipation.

Bio Feedback and Pelvic floor exercises

- Provide significant and durable relief (up to 70%) for persistent lower tract dysfunction.

Drug Treatment

- **Anticholinergics**—Antispasmodic muscarinic effect causing relaxation of bladder smooth muscle.
- **Prophylactic antibiotics.**
- **Onabotulinumtoxin A.**
  - Neurotoxin derived from *Clostridium botulinum*. It prevents Acetylcholine release from the presynaptic membrane preventing detrusor overactivity.
- **Mirabegron.**
  - Is a beta-3 adrenergic receptor agonist that causes relaxation of the detrusor smooth muscle of the urinary bladder and increases bladder capacity.

Intermittent Catheterization and overnight bladder drainage

- Overnight drainage.
  - ↓ upper tract dilatation, ↓ frequency of UTI and improves continence.

- Overnight drainage with **daytime intermittent catheterization (CIC).**
  - Frequency depends on the degree of dysfunction and is appropriate for poorly compliant bladders.
- SPC or Mitrofanoff channel.
  - Can be used to achieve both CIC and overnight bladder drainage.

35.7 Long-Term Management

Depends upon renal function (biochemistry, GFR, etc.), bladder urodynamics studies and upper tract changes. Urodynamics is used to assess bladder capacity, compliance, and voiding dysfunction. Types of urodynamic patterns include:

- Instability.
  - Irregular contractions leading to pain and incontinence.
  - Treatment can be with anticholinergics, e.g., oxybutynin and tolterodine.
- Detrusor sphincter dyssynergia.
  - Bladder contracts against an unrelaxed sphincter and hypertrophic bladder neck.
  - Many children used to go on to have bladder neck incisions which improved voiding symptoms and upper tracts dilatation in some, but in others, it also caused incontinence and retrograde ejaculation. Therefore has fallen out of favor and instead alpha-blockers, e.g., doxazocin, are of help in these cases.
- Hypocontractility.
  - Causes incomplete bladder emptying, ↑resting intra-vesicle pressure, hampering upper tract drainage and increased dilatation of the upper tracts. This can also cause overflow incontinence. This so-called "myogenic failure" has been attributed to long-term obstruction and/or prolonged use of anticholinergics.
  - Usually require CIC but poor compliance due to urethral sensitivity or a catheterizable stoma (e.g., Mitrofanoff).

Children with poor compliance/small volume bladders are candidates for bladder augmentation.

35.7.1 Bladder Dysfunction and the "Valve Bladder"

Voiding dysfunction is extremely common in children with PUV and is secondary to long-standing obstruction and mural hypertrophy and fibrosis. Urodynamic patterns can change over time from bladder instability during infancy to myogenic failure in older boys.

Bladder dysfunction manifesting as incontinence and persistence of upper tract dilatation is being increasingly recognized as one of the factors responsible for eventual renal deterioration. The underlying mechanisms may be:

- Urine concentrating defects.
  - Long-standing back pressure leads to renal tubular dysfunction causing an acquired form of nephrogenic diabetes insipidus.
  - **Polyuria** exacerbates incontinence and upper tract dilatation.
- Persistent upper tract dilation.
- ↑ urine output and hold up at the VUJ—caused by ureter passing through the thick, noncompliant bladder wall.
- Upper tract pressure studies (Whitaker's[3] test) have shown that the VUJ obstruction is not constant but increases as the bladder fills.
- Treatment with ADH for enuresis is not helpful as it is not due to lower ADH production but due to tubular dysfunction (nephrogenic diabetes insipidus).
- ↑ post-void residual (PVR) urine volume due to poor bladder emptying and increased urine production and the upper tract drainage across VUJ is impaired. This leads to more ureteric dilation and further deterioration of tubular function.
- Vesicoureteric reflux.
  - Bilateral in 50%.
  - Reflux subsides with effective valve ablation (~30%).
  - Persistent reflux (~30%).

Persistent VU reflux (despite adequate treatment to lower intravesical pressure by anticholinergic medication or alpha-blocker to improve bladder emptying) can be successfully treated with **STING procedure** in most cases. Ureteric reimplantation in a trabeculated, noncompliant, high-pressure bladder is not recommended as can be fraught with complications in case of re-implanting in a trabeculated, noncompliant, high-pressure bladder (Failure rate 15–30%).

35.7.1.1 VURD Syndrome

In this syndrome, PUV are associated with unilateral **vesicoureteral reflux and renal dysplasia**. The dilated system in these cases acts as a vent for the high-pressure bladder. The pressure "pop-off" mechanism is thought to preserve the function of the contralateral kidney. Nephroureterectomy is usually reserved for cases with recurrent breakthrough UTI with preservation of the dilated ureter to be used for bladder augmentation later on.

35.7.1.2 Hydroureteronephrosis (HUN)

- In almost all cases (96%), there is persistent unilateral HUN and bilateral HUN occurs in 70–80%.
- Glassberg classified hydronephrotic upper tracts into three types with upper tracts that:
  - Drain independent of bladder volume.
  - Drains efficiently only with the bladder empty.
  - That are obstructed independent of bladder volume.
- 45–50% resolves after ablation, nearly 25% will have HUN 5–15 years after ablation.

[3] Robert H. Whitaker—British urologist at Cambridge.

35.8 Long-Term Outcomes

35.8.1 Renal Damage

- Usually Secondary to dysplasia or obstructive uropathy.
- Obstruction and recurrent infections can lead to proteinuria and hyperfiltration.
- Decreased GFR and renal insufficiency occurs.
- Affection of somatic growth and renal development.
- Hypertension.

35.8.2 End-Stage Renal disease

- Occurs in 25–30% of cases.
- Can be due to primary renal dysplasia, as a sequel to bladder outflow obstruction, recurrent UTIs or persistent bladder dysfunction.

Poor Prognostic factors of renal outcome are indicated in Table 35.2.

35.8.3 Renal Transplantation

Up to 30% of children will ultimately require some form of renal replacement therapy culminating in a transplant. Persistent bladder dysfunction not only increases the risk of developing renal failure but has also been shown to decrease graft survival post-transplant.

Table 35.2 Poor prognostic factors in prediction of progression to ESRD

Antenatal factors	Postnatal factors
Gestation at detection (<24 weeks).	Nadir (i.e., lowest possible) serum creatinine – >1 mg/dL (≡ 88 μmol/L) at 1 year of age.
US appearance—cystic changes or echogenic kidneys, imply renal dysplasia.	US appearance: lack of corticomedullary differentiation suggests poor function.
Oligohydramnios / anhydramnios	Incontinence—inability to achieve diurnal continence at 5 years of age.
Fetal urine analysis – Na >100 mmol/L and Cl >90 mmol/L. – β2 microglobulin >40, – urine osmolality >210 mOsm, – urine output <2 ml/h.	Lack of a protective "pop-off" mechanism such as gross unilateral reflux or urinary ascites.
	Presence of severe reflux.

Note: Cobb's (Cobb BG, Wolf JA, Ansell JS (1968) Congenital stricture of the proximal urethral bulb. J Urol; 99:629–631) collar (or congenital urethral stricture)—distal membrane with a central opening within bulbous urethra

35.8.4 Fertility Issues

Diminished fertility possibly due to:

- ↑ posterior urethral pressure *in utero* may affect prostate development.
- ↑ Incidence of undescended testes
- Semen analysis has shown a much thicker ejaculate with decreased sperm motility.
- Voiding dysfunction and retrograde ejaculation.

35.8.5 Urinary Incontinence

Thirty-five percent of patients suffer from constant incontinence and an additional 50% with stress incontinence due to additional bladder neck surgery in the past in addition to ablation of valves. Up to 70% have bladder dysfunction and polyuria due to impaired renal function accounting for incontinence.

35.8.6 Urinary Ascites (5–10%)

Usually secondary to urine leak from a renal fornix blowout, renal parenchymal rupture, or bladder perforation. Abdominal distension can be marked and cause respiratory compromise. Peritoneal absorption of urine can lead to uremia. Paradoxically, urine leaks actually protect the kidneys from the deleterious effects of constant high back pressure from bladder.

35.9 Antenatal Intervention

Controversy surrounds the benefit of antenatal intervention in PUV. However, several variables have been used to determine the prognosis. In essence, a high degree of antenatal dysplasia is associated with poor outcome. This can be assessed by US appearances (Increased echogenicity or cystic changes of Parenchyma, early severe oligohydramnios) and characteristics of fetal urine (Na > 100 mmol/L; osmolality >210 mOSm, protein >20 mg/dl and b2-Microglobulin >4 mg/L).

Types of antenatal interventions include:

- Vesicoamniotic shunts

These shunts are passed percutaneously guided by ultrasound and allow the bladder to decompress in the amniotic cavity. Complications include chorioamnionitis and catheter clogging or displacement and fetal morbidity due to pre-term labor.

A randomized trial comparing this intervention to conservative management **(PLUTO trial)**—although stopped early due to poor recruitment- was able to

conclude that shunting may improve neonatal survival after 28 days (probably due to improvement of oligohydramnios) but did not have an effect on renal parenchymal damage.

- Intrauterine valve ablation

This challenging procedure is done in some specialist centers. However, long-term benefits on progression to ESRD remains questionable.

- Elective preterm delivery or termination of pregnancy

This is the most common antenatal intervention, especially in rapidly progressing disease. In case of pre-term delivery, balancing lung growth with the risk of worsening renal damage is crucial.

- Future Therapeutic Strategies
  - Intra-detrusor botulinum toxin-A injection was found to improve symptoms of urinary frequency and urgency and decrease bladder fibrosis in animal models with BOO.
  - Systemic administration of bone marrow-derived mesenchymal stem cells in animal models with BOO demonstrated short-term urodynamic improvements and significant decrease. in inflammatory mediators.
  - Experimental anti-fibrotic approaches aim to inhibit cytokines, chemokines, specific matrix metallopeptidases and collagen synthesis.

Further Reading

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