

Guidelines on Paediatric Urology

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1. INTRODUCTION

A collaborative working group consisting of members representing the European Society for Paediatric Urology (ESPU) and the European Association of Urology (EAU) has gathered in an effort to produce the current update of the paediatric urology guidelines. The aim of this close collaboration between a subspecialty group and its parent specialty is to make a document available that may help to increase the quality of care for children with urological problems.

The majority of urological clinical problems in children are distinct and in many ways different to those in adults. The aim of this work is to outline a practical and preliminary approach to paediatric urological problems. Complex and rare conditions that require special care with experienced doctors should be referred to designated centres where paediatric urology practice has been fully established and a multidisciplinary approach is available.

For quite some time, paediatric urology has informally developed, expanded, matured and established its diverse body of knowledge and expertise and may now be ready to distinguish itself from its parent specialties. Thus, paediatric urology has recently emerged in many European countries as a distinct subspecialty of both urology and paediatric surgery, and presents a unique challenge in the sense that it covers a large area with many different schools of thought and a huge diversity in management.

Knowledge gained by increasing experience, new technological advances and non-invasive diagnostic screening modalities has had a profound influence on treatment modalities in paediatric urology, a trend that is likely to continue in the years to come. We now have new techniques for the treatment of reflux, our techniques for the treatment of complex congenital anomalies have substantially improved and totally new technologies for bladder replacement and laparoscopic procedures have been developed. There is also an increasing body of knowledge in paediatric urology related to basic research.

Paediatric urology covers a huge field within urology. The scope and complexity of paediatric urology practice continues to expand. Capturing the entire field of paediatric urology in a single guideline document was never an option, but we will keep on amending and adding on this document on a regular basis. This year there are two new chapters within the document and eight chapters have been revised.

The guidelines were compiled by the collaborative working group and based on current literature following a systematic review using MEDLINE. Application of a structured analysis of the literature was not possible in many conditions due to a lack of well-designed studies. Whenever possible, statements have been classified in terms of level of evidence and grade of recommendation (1). Due to the limited availability of large randomised controlled trials – influenced also by the fact that a considerable number of treatment options relate to surgical interventions on a large spectrum of different congenital problems – this document will therefore largely be a consensus document.

We hope that you will consider this document to be a valuable educational resource for your practice and that it will provide you with guidance in the care of your cases in paediatric urology.

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2. PHIMOSIS

2.1 Background

At the end of the first year of life, retraction of the foreskin behind the glandular sulcus is possible in only about 50% of boys; this rises to approximately 89% by the age of 3 years. The incidence of phimosis is 8% in 6 to 7-year-olds and just 1% in males aged 16-18 years (1). The phimosis is either primary (physiological) with no sign of scarring, or secondary (pathological) to a scarring such as balanitis xerotica obliterans. Phimosis has to be distinguished from normal agglutination of the foreskin to the glans, which is a physiological phenomenon (2).

The paraphimosis must be regarded as an emergency situation: retraction of a too narrow prepuce behind the glans penis into the glandular sulcus may constrict the shaft and lead to oedema. It interferes with perfusion distally from the constrictive ring and brings a risk of consecutive necrosis.

2.2 Diagnosis

The diagnosis of phimosis and paraphimosis is made by physical examination.

If the prepuce is not retractable or only partly retractable and shows a constrictive ring on drawing back over the glans penis, a disproportion between the width of the foreskin and the diameter of the glans penis has to be assumed. In addition to the constricted foreskin, there may be adhesions between the inner surface of the prepuce and the glanular epithelium and/or a fraenum breve. A fraenum breve leads to a ventral deviation of the glans once the foreskin is retracted. If the tip remains narrow and glanular adhesions were separated, than the space is filled with urine during voiding causing the foreskin to balloon outward.

The paraphimosis is characterised by retracted foreskin with the constrictive ring localised at the level of the sulcus, which prevents replacement of the foreskin over the glans.

2.3 Treatment

Treatment of phimosis in children is dependent on the parents' preferences and can be plastic or radical circumcision after completion of the second year of life. Plastic circumcision has the objective of achieving a wide foreskin circumference with full retractability, while the foreskin is preserved (dorsal incision, partial circumcision). However, this procedure carries the potential for recurrence of the phimosis. In the same session, adhesions are released and an associated fraenum breve is corrected by fraenulotomy. Meatoplasty is added if necessary.

An absolute indication for circumcision is secondary phimosis. The indications in primary phimosis are recurrent balanoposthitis and recurrent urinary tract infections in patients with urinary tract abnormalities (3-6) (LE: 2, GR: B). Simple ballooning of the foreskin during micturition is not a strict indication for circumcision.

Routine neonatal circumcision to prevent penile carcinoma is not indicated. Contraindications for circumcision are coagulopathy, an acute local infection and congenital anomalies of the penis, particularly hypospadias or buried penis, because the foreskin may be required for a reconstructive procedure (7, 8). Childhood circumcision has an appreciable morbidity and should not be recommended without a medical reason (9-12) (LE: 2, GR: B). As a conservative treatment option of the primary phimosis, a corticoid ointment or cream (0.05-0.1%) can be administered twice a day over a period of 20-30 days (13-16) (LE: 1, GR: A). This treatment has no side effects and the mean bloodspot cortisol levels are not significantly different from an untreated group of patients (17) (LE: 1). Agglutination of the foreskin does not respond to steroid treatment (14) (LE: 2).

Treatment of paraphimosis consists of manual compression of the oedematous tissue with a subsequent attempt to retract the tightened foreskin over the glans penis. Injection of hyaluronidase beneath the narrow band may be helpful to release it (18) (LE: 4, GR: C). If this manoeuvre fails, a dorsal incision of the constrictive ring is required. Depending on the local findings, a circumcision is carried out immediately or can be performed in a second session.

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3. CRYPTORCHIDISM

3.1 Background

At 1 year of age, nearly 1% of all full-term male infants have cryptorchidism, which is the commonest congenital anomaly affecting the genitalia of newborn males (1). The most useful classification of cryptorchidism is into palpable and non-palpable testes, as clinical management is decided by the location and existence of the testis.

- Retractable testes require only observation as they may become ascendant. Although they have completed their descent, a strong cremasteric reflex may cause their retention in the groin (2).
- Bilateral, non-palpable testes and any suggestion of sexual differentiation problems (e.g. hypospadias) require urgent, mandatory endocrinological and genetic evaluation (3) (LE: 3; GR: B).

3.2 Diagnosis

A physical examination is the only way of differentiating between palpable or non-palpable testes. There is no benefit in performing ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) or angiography.

Clinical examination includes a visual description of the scrotum and an examination of the child in both a supine and crossed-leg position. The examiner should inhibit the cremasteric reflex with his non-dominant hand, immediately above the symphysis in the groin region, before touching, or reaching for, the scrotum. The groin region may be 'milked' towards the scrotum in an attempt to move the testis into the scrotum. This manoeuvre also allows an inguinal testis to be differentiated from enlarged lymph nodes that could give the impression of an undescended testis. A retractile testis can generally be brought into the scrotum, where it will remain until a cremasteric reflex (touching the inner thigh skin) will retract it again into the groin (4).

A unilateral, non-palpable testis and an enlarged contralateral testis may suggest testicular absence or atrophy, but this is not a specific finding and does not preclude surgical exploration. An inguinal, non-palpable testis

requires specific visual inspection of the femoral, penile and perineal region to exclude an ectopic testis.

Diagnostic laparoscopy is the only examination that can reliably confirm or exclude an intra-abdominal, inguinal and absent/vanishing testis (non-palpable testis) (5) (LE: 1b; GR: A). Before carrying out laparoscopic assessment, an examination under general anaesthesia is recommended because some, originally non-palpable, testes become palpable under anaesthetic conditions.

3.3 Treatment

If a testis has not descended by the age of 1 year, there is no benefit in waiting for a spontaneous descent. To prevent histological deterioration, treatment should be carried out and finished before 12-18 months of age (6).

3.3.1 Medical therapy

Medical therapy using human chorionic gonadotrophin (hCG) or gonadotrophin-releasing hormone (GnRH) is based on the hormonal dependence of testicular descent with maximum success rates of 20% (7,8). Hormonal therapy for testicular descent has lower success rates, the higher the undescended testis is located. A total dose of 6.000 to 9.000 units of hCG is given in four doses over a period of 2 to 3 weeks depending on weight and age, along with GnRH, given for 4 weeks as a nasal spray in a dose of 1.2 mg/day, divided into three doses per day.

Medical treatment may be beneficial before surgical orchidolysis and orchidopexy (dosage as described earlier) or afterwards (low intermittent dosages) (14), in terms of increasing the fertility index, which is a predictor for fertility in later life (14). However, long-term follow-up data are awaited.

3.3.2 Surgery

Palpable testis: surgery for the palpable testis includes orchidofuniculolysis and orchidopexy, via an inguinal approach, with success rates of up to 92% (9). It is important to remove and dissect all cremasteric fibres to prevent secondary retraction. Associated problems, e.g. an open processus vaginalis, must be carefully dissected and closed. It is recommended that the testis is placed in a subdartos pouch. With regard to sutures, there should either be no fixation sutures or they should be made between the tunica vaginalis and the dartos musculature.

The lymph drainage of a testis that has undergone surgery for orchidopexy has been changed from iliac drainage to iliac and inguinal drainage (important in the event of later malignancy).

Non-palpable testis: inguinal surgical exploration with possible laparoscopy should be attempted. There is a significant chance of finding the testis via an inguinal incision. In rare cases, it is necessary to search into the abdomen if there are no vessels or vas deferens in the groin. Laparoscopy is the best way of examining the abdomen for a testis. In addition, either removal or orchidolysis and orchidopexy can be performed via laparoscopic access (10). Before starting diagnostic laparoscopy, examine the child under general anaesthesia since a previously non-palpable testes might now be palpable under anaesthesia.

An intra-abdominal testis in a 10-year-old boy or older, with a normal contralateral testis, should be removed. In bilateral intra-abdominal testes, or in a boy younger than 10 years, a one-stage or two-stage Fowler-Stephens procedure can be performed. In the event of a two-stage procedure, the spermatic vessels are either laparoscopically clipped or coagulated proximal to the testis to allow development of collateral vasculature (11). The second-stage procedure, in which the testis is brought directly over the symphysis and next to the bladder into the scrotum, can also be performed by laparoscopy 6 months later. The testicular survival rate in a one-stage procedure varies between 50% and 60%, with success rates rising up to 90% in a two-stage procedure (12). Microvascular autotransplantation can also be performed with a 90% testicular survival rate. However, the procedure requires very skilful and experienced surgical techniques (13).

3.4 Prognosis

Although boys with one undescended testis have a lower fertility rate, they have the same paternity rate as boys with bilateral descended testes. Boys with bilateral undescended testes have a lower fertility and paternity rate.

Boys with an undescended testis have a 20-fold higher risk of developing testicular malignancy, a risk uninfluenced by any kind of treatment. Screening both during and after puberty is therefore recommended for these boys. Recently, a Swedish study, with a cohort of almost 17,000 men who were treated surgically for undescended testis and followed for a total of almost 210,000 person years, showed that treatment for

undescended testis before puberty decreased the risk of testicular cancer. The relative risk of testicular cancer among those who underwent orchiopexy before 13 years of age was 2.23 when compared with the Swedish general population; this increased to 5.40 for those treated at 13 years of age or older 5.40 (15). A systematic review and meta-analysis of the literature by an American group has also concluded that prepubertal orchiopexy may decrease the risk of testicular cancer and that early surgical intervention is indicated in children with cryptorchidism (16).

Boys with retractile testes do not need medical or surgical treatment, but require close follow-up until puberty.

3.5 Recommendations for cryptorchidism

Recommendations
Due to the lack of spontaneous testicular descent after the age of 1 year, and because of the potential loss of testicular quality, it is recommended that surgical orchidolysis and orchidopexy should be performed at the latest by 12-18 months of age.
To date, it seems that pre- or post-operative hormonal treatment may have a beneficial effect on fertility later in life.

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4. HYDROCELE

4.1 Background

Hydrocele is defined as a collection of fluid between the parietal and visceral layer of tunica vaginalis (1). Pathogenesis of hydrocele is based on an imbalance between the secretion and reabsorption of this fluid. This is in contrast with inguinal hernia, which is defined as the protrusion of a portion of organs or tissues through the abdominal wall (2). Incomplete obliteration of the processus vaginalis peritonei results in formation of various types of communicating hydrocele alone or connected with other intrascrotal pathology (hernia). The exact time of obliteration of processus vaginalis is not known. It persists in approximately 80-94% of newborns and in 20% of adults (3). If complete obliteration of processus vaginalis occurs with patency of midportion, a hydrocele of the cord occurs. Scrotal hydroceles without associated patency of the processus vaginalis are encountered in newborns as well (4). Non-communicating hydroceles are found secondary to minor trauma, testicular torsion, epididymitis, varicocele operation or may appear as a recurrence after primary repair of a communicating hydrocele.

4.2 Diagnosis

The classic description of a communicating hydrocele is that of a hydrocele that vacillates in size, and is usually related to activity. It may be diagnosed by history; physical investigation and transillumination of the scrotum make the diagnosis in the majority of cases (5). If the diagnosis is that of a hydrocele, there will be no history of reducibility and no associated symptoms; the swelling is translucent, smooth and usually non-tender. If there are any doubts about the character of an intrascrotal mass, scrotal ultrasound should be performed and has nearly 100% sensitivity in detecting intrascrotal lesions. Doppler ultrasound studies help to distinguish hydroceles from varicocele and testicular torsion, although these conditions may also be accompanied by a hydrocele.

4.3 Treatment

In the majority of infants, the surgical treatment of hydrocele is not indicated within the first 12-24 months because of the tendency for spontaneous resolution (LE: 4, GR: C). Early surgery is indicated if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology (6). The question of contralateral disease should be addressed by both history and examination at the time of initial consultation (5). Persistence of a simple scrotal hydrocele beyond 24 months of age may be an indication for surgical correction. However, there is no evidence that this type of hydrocele risks testicular damage. In the paediatric age group, the operation consists of ligation of patent processus vaginalis via inguinal incision and the distal stump is left open, whereas in hydrocele of the cord the cystic mass is excised or unroofed (1,5,6) (LE: 4, GR: C). In expert hands, the incidence of testicular damage during hydrocele or inguinal hernia repair is very low (0.3%) (LE: 3, GR: B). Sclerosing agents should not be used because of the risk of chemical peritonitis in communicating processus vaginalis peritonei (5,6) (LE: 4, GR: C). The scrotal approach (Lord or Jaboulay technique) is used in the treatment of a secondary non-communicating hydrocele.

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5. ACUTE SCROTUM IN CHILDREN

5.1 Background

Acute scrotum is a paediatric urology emergency case, most commonly caused by torsion of the testis, torsion of the appendix testis and epididymitis/epididymo-orchitis (1-6). Other causes of acute scrotal pain are idiopathic scrotal oedema, mumps orchitis, varicocele, scrotal haematoma, incarcerated hernia, appendicitis or systemic disease (Henoch-Schönlein purpura) (7-19).

Torsion of the testis occurs most often in the neonatal period and around puberty, while torsion of the appendix testes occurs over a wider age range. Acute epididymitis affects two age groups: below the age of 1 year and between 12 and 15 years (5,20,21). Acute epididymitis was found most often (37-64.6%) in boys with acute scrotum (1-4). One study predicted the incidence of epididymitis as about 1.2 per 1,000 male children per year (22).

5.2 Diagnosis

Patients usually present with scrotal pain. The duration of symptoms is shorter in testicular torsion (69% present within 12 hours) compared to torsion of the appendix testes (62%) and acute epididymitis (31%) (5,6,20).

In the early phase, location of the pain can lead to the diagnosis. Patients with acute epididymitis experience a tender epididymitis, while patients with testicular torsion are more likely to have a tender testicle and patients with torsion of the appendix testis feel isolated tenderness of the superior pole of the testis (20).

An abnormal position of the testis was more frequent in testicular torsion than in patients with epididymitis (20). Looking for the absence of the cremasteric reflex is a simple method with a sensitivity of 100% and specificity of 66% for the presence of testicular torsion (21,23) (LE: 3; GR: C).

Fever occurs often in epididymitis (11-19%). The classical sign of a 'blue dot' was found only in 10-23% patients with torsion of the appendix testis (4,6,21,24).

In many cases, it is not easy to determine the cause of acute scrotum based on history and physical examination alone (1-6,21,24).

A positive urine culture is only found in a few patients with epididymitis (3,21,24,25). It should be remembered that a normal urinalysis does not exclude epididymitis. Similarly, an abnormal urinalysis does not exclude testicular torsion.

Doppler ultrasound is useful to evaluate an acute scrotum, with a sensitivity of 63.6-100% and a specificity of 97-100%, and a positive predictive value of 100% and negative predictive value 97.5% (26-31) (LE: 3; GR: C). The use of Doppler ultrasound may reduce the number of patients with acute scrotum undergoing scrotal exploration, but it is operator-dependent and can be difficult to perform in prepubertal patients (29, 32). It may also show a misleading arterial flow in the early phases of torsion and in partial or intermittent torsion: persistent arterial flow does not exclude testicular torsion. In a multicentre study of 208 boys with torsion of the testis, 24% patients had normal or increased testicular vascularisation (29). Better results were reported using high-resolution ultrasonography (HRUS) for direct visualisation of the spermatic cord twist with a sensitivity of 97.3% and a specificity of 99% (29,33) (LE: 2; GR: C).

Scintigraphy and, more recently, dynamic contrast-enhanced subtraction MRI of the scrotum also provide a comparable sensitivity and specificity to ultrasound (34-37). These investigations may be used when diagnosis is less likely and if torsion of the testis still cannot be excluded from history and physical examination. This should be done without inordinate delays for emergent intervention (24).

The diagnosis of acute epididymitis in boys is mainly based on clinical judgement and adjunctive investigation. However, it should be remembered that findings of secondary inflammatory changes in the absence of evidence of an extra-testicular nodule by Doppler ultrasound might suggest an erroneous diagnosis of epididymitis in children with torsion of appendix testes (38).

Prepubertal boys with acute epididymitis have an incidence of underlying urogenital anomalies of 25-27.6%. Complete urological evaluation in all children with acute epididymitis is still debatable (3,21,22).

5.3 Treatment

5.3.1 Epididymitis

In prepubertal boys, the aetiology is usually unclear, with an underlying pathology of about 25%. A urine culture is usually negative, and unlike in older boys, a sexually transmitted disease is very rare.

Antibiotic treatment, although often started, is not indicated in most cases unless urinalysis and urine culture show a bacterial infection (22,39). Epididymitis is usually self-limiting and with supportive therapy (i.e. minimal physical activity and analgesics) heals without any sequelae (LE: 3; GR: C). However, bacterial epididymitis can be complicated by abscess or necrotic testis and surgical exploration is required (40).

Torsion of the appendix testis can be managed conservatively (LE: 4; GR: C). During the six-week follow-up, clinically and with ultrasound, no testicular atrophy was revealed. Surgical exploration is done in equivocal cases and in patients with persistent pain (27).

5.3.2 Testicular torsion

Manual detorsion of the testis is done without anaesthesia. It should initially be done by outwards rotation of the testis unless the pain increases or if there is obvious resistance. Success is defined as the immediate relief of all symptoms and normal findings at physical examination (41) (LE: 3; GR: C). Doppler ultrasound may be used for guidance (42).

Bilateral orchiopexy is still required after successful detorsion. This should not be done as an elective procedure, but rather immediately following detorsion. One study reported residual torsion during exploration in 17 out of 53 patients, including 11 patients who had reported pain relief after manual detorsion (41,43).

5.3.3 Surgical treatment

Testicular torsion is an urgent condition, which requires prompt surgical treatment. The two most important determinants of early salvage rate of the testis are the time between onset of symptoms and the detorsion and degree of twisting of the cord (44). Severe testicular atrophy occurred after torsion for as little as 4 hours when the turn was more than 360°. In cases of incomplete torsion (180° to 360°), with symptom duration up to 12 hours, no atrophy was observed. However, an absent or severely atrophied testis was found in all cases of torsion of more than 360° and symptom duration of more than 24 hours (45).

Early surgical intervention with detorsion (mean torsion time < 13 hours) was found to preserve fertility (46). Urgent surgical exploration is mandatory in all cases of testicular torsion within 24 hours of the onset of symptoms.

In those patients with testicular torsion of more than 24 hours, semi-elective exploration is necessary (44,45) (LE: 3; GR: C). Until now, there is still controversy to carry out detorsion and to preserve the ipsilateral testis, or to perform an orchiectomy, in order to preserve contralateral function and fertility after testicular torsion of long duration (> 24 hours).

A recent study in humans found that sperm quality was preserved in both orchiectomy and orchiopexy groups in comparison to control normal men, although orchiectomy resulted in better sperm morphology (47).

During exploration, fixation of the contralateral testis is also performed. Recurrence after orchiopexy is rare (4.5%) and may occur several years after operation. There is no common recommendation about the preferred type of fixation and suture material; however, many urologists currently use a Dartos pouch orchiopexy (48).

External cooling before exploration and several medical treatments seem effective in reducing ischaemia-reperfusion injury and preserving the viability of the torsed testis and the contralateral testis (49-53).

5.4 Prognosis

5.4.1 Fertility

The results vary and are conflicting. In one study, unilateral torsion of the testis seriously intervened with subsequent spermatogenesis in about 50% of the patients and produced borderline impairment in another 20%.

5.4.2 Subfertility

Subfertility is found in 36-39% of the patients after torsion. Semen analysis may be normal in only 5-50% in long-term follow-up (44). Early surgical intervention (mean torsion time < 13 hours) with detorsion was found to preserve fertility, but prolonged torsion periods (mean torsion time of 70 hours) followed by orchiectomy jeopardises fertility (46).

One study identified antisperm antibodies in the semen of patients with testicular torsion and correlated antibody levels with infertility, while other studies have failed to confirm these results (44,47).

Anderson et al. found pre-existing contralateral testis abnormalities in biopsies performed at the time of surgery and did not detect any case of antisperm antibodies after testicular torsion (46).

5.4.3 **Androgen levels**

A study in rats showed a long-term reduction in testicular androgen production after testicular torsion. This effect was considered to be caused by reperfusion/ oxidative stress in the testis (45). Even though the levels of FSH, LH and testosterone are higher in patients after testicular torsion compared to normal controls, endocrine testicular function remains in the normal range in patients after testicular torsion (47).

5.4.4 **Testicular cancer**

There may be a 3.2-fold increased risk of developing a testis tumour 6-13 years after torsion. However, two of nine reported cases had torsion of a tumour-bearing testis and four had a tumour in the contralateral testis to the torsed testicle (44).

5.4.5 **Nitric oxide**

A study in rats found that spermatic cord torsion did not lead to impairment in nitric oxide-mediated relaxant responses of the isolated penile bulb (54).

5.5 **Perinatal torsion**

Perinatal torsion of the testis most often occurs prenatally. After birth, perinatal torsion occurs in 25%, with bilateral perinatal torsion comprises 11-21% of all perinatal torsions (55). Most cases are extravaginal torsion in contrast to the usual intravaginal torsion, which occurs during puberty.

Intrauterine torsion may present as:

- Patients with a testicular nubbin
- Patients with a small and hard testis
- Patients with a normal-sized and hard testis
- Patients with an acute scrotum.

Torsion occurring in the postnatal period within the first month of life presents with signs of an acute scrotum. The clinical signs correlate well with surgical and histological findings and thus define the need and the urgency to explore the history (56). Doppler ultrasound can be an additional diagnosis tool. The sensitivity for diagnosis of torsion of the testis is high, though the specificity is unknown for neonates. Doppler ultrasound may also be used to exclude congenital testicular neoplasm (57). Neonates with acute scrotal signs as well as bilateral cases should be treated as surgical emergencies (56,58).

In cases of postnatal torsion, one study reported 40% of testes were salvaged with emergency exploration (59). The contralateral scrotum should also be explored because of the risk of asynchronous contralateral testicular torsion in as many as 33% of cases (58).

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6. HYPOSPADIAS

6.1 Background

Hypospadias can be defined as hypoplasia of the tissues forming the ventral aspect of the penis beyond the division of the corpus spongiosum. Hypospadias are usually classified based on the anatomical location of the proximally displaced urethral orifice:

- Distal-anterior hypospadias (located on the glans or distal shaft of the penis and the most common type of hypospadias)
 - Intermediate-middle (penile)
 - Proximal-posterior (penoscrotal, scrotal, perineal).
- The pathology may be much more severe after skin release.

6.1.1 Risk factors

Risk factors associated with hypospadias are likely to be genetic, placental and/or environmental (1) (LE: 2b):

- Endocrine disorders can be detected in a very few cases.
- Babies of young or old mothers and babies with a low birth weight have a higher risk of hypospadias.
- A significant increase in the incidence of hypospadias over the last 20 years suggests a role for

environmental factors (hormonal disruptors and pesticides) (2-5).

The use of oral contraceptives prior to pregnancy has not been associated with an increased risk of hypospadias in the offspring (6) (LE: 2a; GR: B).

6.2 Diagnosis

Patients with hypospadias should be diagnosed at birth (except for the megameatus intact prepuce variant).

Diagnosis includes a description of the local findings:

- Position, shape and width of the orifice
- Presence of atretic urethra and division of corpus spongiosum
- Appearance of the preputial hood and scrotum
- Size of the penis
- Curvature of the penis on erection.

The diagnostic evaluation also includes an assessment of associated anomalies, which are:

- Cryptorchidism (in up to 10% of cases of hypospadias)
- Open processus vaginalis or inguinal hernia (in 9-15%).

Severe hypospadias with unilaterally or bilaterally impalpable testis, or with ambiguous genitalia, require a complete genetic and endocrine work-up immediately after birth to exclude intersexuality, especially congenital adrenal hyperplasia.

Urine trickling and ballooning of the urethra requires exclusion of meatal stenosis.

The incidence of anomalies of the upper urinary tract does not differ from the general population, except in very severe forms of hypospadias (2, 3).

6.3 Treatment

Differentiation between functionally necessary and aesthetically feasible operative procedures is important for therapeutic decision-making.

The functional indications for surgery are:

- Proximally located meatus
- Ventrally deflected urinary stream
- Meatal stenosis
- Curved penis.

The cosmetic indications, which are strongly linked to the psychology of the parent or future patient's psychology, are:

- Abnormally located meatus
- Cleft glans
- Rotated penis with abnormal cutaneous raphe
- Preputial hood
- Penoscrotal transposition
- Split scrotum.

As all surgical procedures carry the risk of complications, thorough pre-operative counselling of the parents is crucial.

The therapeutic objectives are to correct the penile curvature, to form a neo-urethra of an adequate size, to bring the neomeatus to the tip of the glans, if possible, and to achieve an overall acceptable cosmetic appearance of the boy's genitalia (2,3) (LE: 4; GR: C) (Figure 1).

The use of magnifying spectacles and special fine synthetic absorbable suture materials (6/0-7/0) is required. As in any penile surgery, an exceptional prudence should be adopted with the use of cautery. Knowledge of a variety of surgical reconstructive techniques, wound care and post-operative treatment are essential for a satisfactory outcome. Pre-operative hormonal treatment with local or parenteral application of testosterone, dihydrotestosterone or beta-chorionic gonadotropin can be helpful in patients with a small penis or for repeat surgery.

6.3.1 Age at surgery

The age at surgery for primary hypospadias repair is usually 6-18 (7) months (2) (LE: 4; GR: C). However, earlier repair between 4 and 6 months of age has been reported recently (LE: 3; GR: B) (8).

6.3.2 Penile curvature

If present, penile curvature is often released by degloving the penis (skin chordee) and by excision of the connective tissue of the genuine chordee on the ventral aspect of the penis. The urethral plate has well-vascularised connective tissue and does not cause curvature in most cases. The residual chordee (curvature) is caused by corporeal disproportion and requires straightening of the penis, mostly using dorsal orthoplasty (modification of Nesbit dorsal corporeal plication) (9) (LE: 3; GR: B).

6.3.3 Preservation of the well-vascularised urethral plate

The mainstay of hypospadias repair is preservation of the well-vascularised urethral plate and its use for urethral reconstruction has become the mainstay of hypospadias repair (10).

If the urethral plate is wide, it can be tubularised following the Thiersch-Duplay technique. If the plate is too narrow to be simply tubularised, it is recommended that a midline-relaxing incision of the plate, followed by reconstruction according to the Snodgrass-Orkiszewski technique, is performed in distal hypospadias, as well as in proximal hypospadias (though the complication rate is higher) (7,11-15).

The onlay technique is preferred in proximal hypospadias and in cases of a plate that is unhealthy or too narrow. For distal forms of hypospadias, a range of other techniques is available (e.g. Mathieu, urethral advancement, etc) (12,16) (LE: 2b; GR: B).

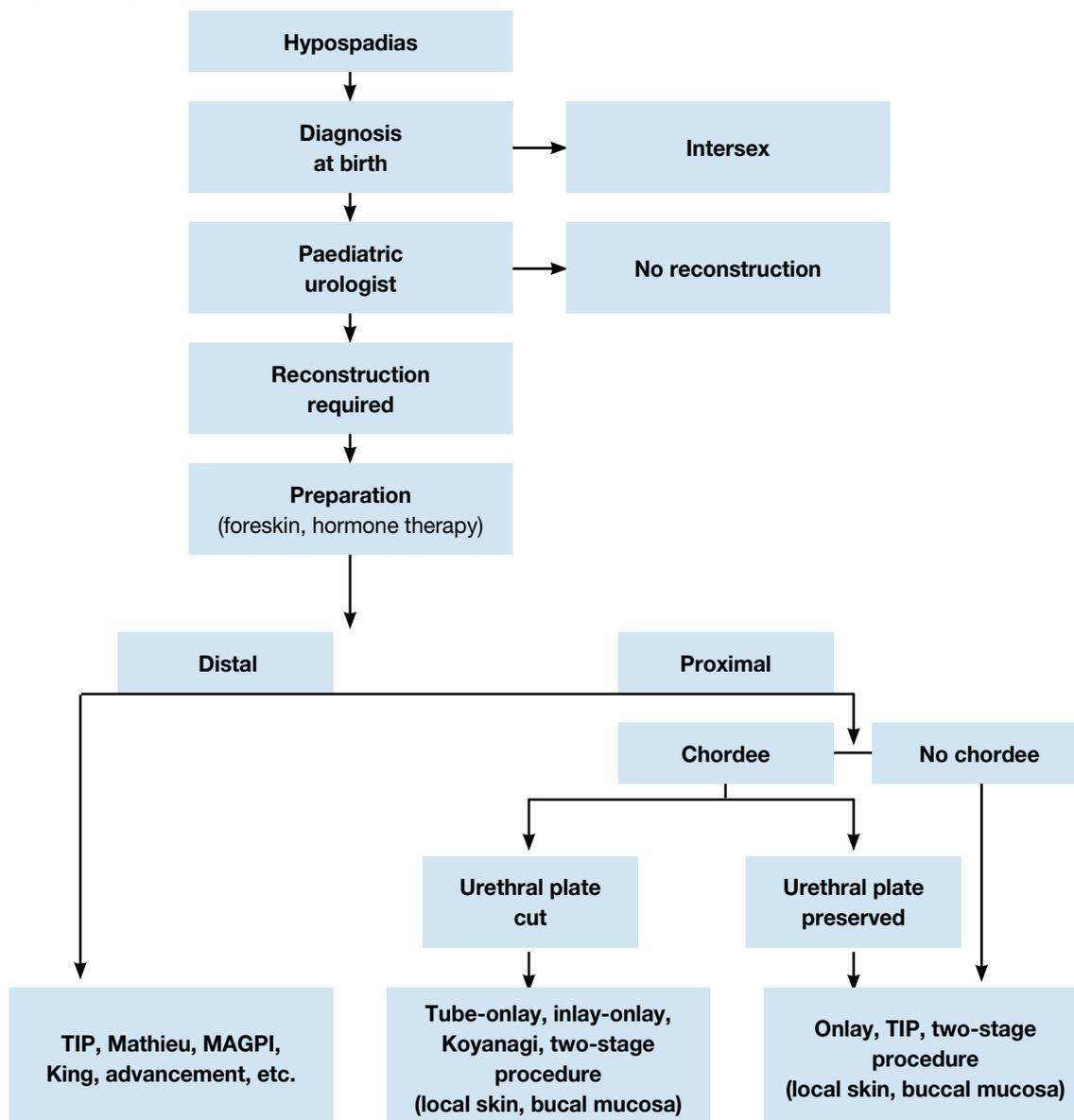
If the continuity of the urethral plate cannot be preserved, a modification of the tubularised flap, such as a tube-onlay or an inlay-onlay flap, is used to prevent urethral stricture (17,18) (LE: 3; GR: C). In this situation, as well as in severe scrotal or penoscrotal hypospadias, the Koyanagi technique or two-stage procedure may be an option (19-21).

If preputial or penile skin is not available, or has signs of balanitis xerotica obliterans, a buccal mucosa graft is used in an onlay or two-stage repair (22-25) (LE: 3; GR: C). The use of inlay skin grafts may allow an increased number of single-stage repairs to be performed (26, 27).

6.3.4 Re-do hypospadias repairs

For re-do hypospadias repairs, no definitive guidelines can be given. All the above-mentioned procedures are used in different ways and are often modified according to the individual needs of the patient.

Figure 1: Algorithm for the management of hypospadias



TIP = tubularised incised plate urethroplasty; MAGPI = meatal advancement and granuloplasty.

6.3.5 Urethral reconstruction

Following formation of the neo-urethra, the procedure is completed by glansplasty and by reconstruction of the penile skin. If there is a shortage of skin covering, the preputial double-face technique or placement of the suture line into the scrotum may be used. In countries where circumcision is not routinely performed, preputial reconstruction can be considered. However, in the TIP repair, the parents should be advised that use of a preputial dartos flap reduces the fistula rate (11) (LE: 2; GR: B).

6.3.6 Urine drainage and wound dressing

Urine is drained with a transurethral dripping stent, or with a suprapubic tube. Some surgeons use no drainage after distal hypospadias repair. Circular dressing with slight compression, as well as prophylactic antibiotics, are established procedures.

A large variety of duration of stenting and dressing is described. No recommendation can be given due to the low level of evidence.

6.3.7 Outcome

Adolescents, who have undergone hypospadias repair in childhood, have a slightly higher rate of dissatisfaction with penile size, but their sexual behaviour is not different from that in control subjects (28) (LE: 2a).

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7. CONGENITAL PENILE CURVATURE

7.1 Background

Penile curvature may be ventral, dorsal or lateral. Most of ventral curvatures are associated with hypospadias due to chordee or ventral dysplasia of cavernous bodies (1). Similarly, the dorsal curvature is mostly associated with epispadias (2). Isolated penile curvature is not frequent with an incidence of 0.6 % (3) (LE: 2). The curvature is caused by asymmetry of the cavernous bodies (1,4).

Curvature over 30 degrees is considered clinically significant; curvature over 60 degrees may interfere with satisfactory sexual intercourse in adulthood (5) (LE: 4).

7.2 Diagnosis

Diagnosis is made during hypospadias or epispadias repair using an artificial erection (6). The isolated anomaly is usually not recognised until later in childhood because the appearance of the penis is normal. The curvature is only observed during erections.

7.3 Treatment

The treatment is surgical. An artificial erection is used to determine the degree of curvature and to check the symmetry after the repair (6).

In hypospadias, chordee related to the tethering of the ventral skin and to the spongiosal pillars is first released. Only in a few cases the penile curvature is caused by a short urethral plate, which should be cut.

To repair the corporeal angulation in the isolated curvature or curvature associated with hypospadias, different techniques of plication of corpora cavernosa (orthoplasty) are used (5).

In epispadias, a combination of complete release of the urethral body from the corpora and a different kind of corporoplasty with or without corporotomy is usually necessary to achieve a straight penis (7,8).

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8. VARICOCELE IN CHILDREN AND ADOLESCENTS

8.1 Background

Varicocele is defined as an abnormal dilatation of testicular veins in the pampiniformis plexus caused by venous reflux. It is unusual in boys under 10 years of age and becomes more frequent at the beginning of puberty. It is found in 15-20% of adolescents, with a similar incidence during adulthood. It appears mostly on the left side (78-93% of cases). Right-sided varicoceles are least common; they are usually noted only when bilateral varicoceles are present and seldom occur as an isolated finding (1,2).

Varicocele develops during accelerated body growth by a mechanism that is not clearly understood. Varicocele can induce apoptotic pathways because of heat stress, androgen deprivation and accumulation of toxic materials. Severe damage is found in 20% of adolescents affected, with abnormal findings in 46% of affected adolescents. Histological findings are similar in children or adolescents and in infertile men. In 70% of patients with grade II and III varicocele, left testicular volume loss was found. However, studies correlating a hypoplastic testicle with poor sperm quality have reported controversial results (3,4).

Several authors reported on reversal of testicular growth after varicocelectomy in adolescents (LE: 2) (5,6). However, this may partly be attributable to testicular oedema associated with the division of lymphatic vessels (LE: 2) (7).

In about 20% of adolescents with varicocele, fertility problems will arise (8). The adverse influence of varicocele increases with time. Improvement in sperm parameters has been demonstrated after adolescent varicocelectomy (LE: 1) (3,9).

8.2 Diagnosis

Varicocele is mostly asymptomatic, rarely causing pain at this age. It may be noticed by the patient or parents, or discovered by the paediatrician at a routine visit. The diagnosis depends upon the clinical finding of a collection of dilated and tortuous veins in the upright posture; the veins are more pronounced when the patient performs the Valsalva manoeuvre.

Varicocele is classified into 3 grades: Grade I - Valsalva positive (palpable at Valsalva manoeuvre only); Grade II - palpable (palpable without the Valsalva manoeuvre); Grade III - visible (visible at distance) (10). The size of both testicles should be evaluated during palpation to detect a smaller testis.

Venous reflux into the plexus pampiniformis is diagnosed using Doppler colour flow mapping in the supine and upright position (11). Venous reflux detected on ultrasound only is classified as subclinical varicocele. The ultrasound examination includes assessment of the testicular volume to discriminate testicular hypoplasia. In adolescents, a testis that is smaller by more than 2 mL compared to the other testis is considered to be hypoplastic (LE: 4) (1).

In order to assess testicular injury in adolescents with varicocele, supranormal follicle-stimulating hormone (FSH) and luteinising hormone (LH) responses to the luteinising hormone-releasing hormone (LHRH) stimulation test are considered reliable, as histopathological testicular changes have been found in these patients (9,12).

8.3 Therapy

Surgical intervention is based on ligation or occlusion of the internal spermatic veins. Ligation is performed at different levels:

- inguinal (or subinguinal) microsurgical ligation
- suprainguinal ligation, using open or laparoscopic techniques (13-16).

The advantage of the former is the lower invasiveness of the procedure, while the advantage of the latter is a considerably lower number of veins to be ligated and safety of the incidental division of the internal spermatic artery at the suprainguinal level.

For surgical ligation, some form of optical magnification (microscopic or laparoscopic magnification) should be used because the internal spermatic artery is 0.5 mm in diameter at the level of the internal ring (13-15,17). The recurrence rate is usually less than 10%. Angiographic occlusion is based on retrograde or antegrade sclerotisation of the internal spermatic veins (18,19).

Lymphatic-sparing varicocelectomy is preferred to prevent hydrocele formation and testicular hypertrophy development and to achieve a better testicular function according to the LHRH stimulation test (LE: 2; GR: A) (7,13,16,17,20). The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs, or suprainguinal open or laparoscopic lymphatic-sparing repairs.

Angiographic occlusion of the internal spermatic veins also meets these requirements. However, although this method is less invasive, it appears to have a higher failure rate (LE: 2; GR: B) (1,19).

There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later. The recommended indication criteria for varicocelectomy in children and adolescents are (1,21):

- varicocele associated with a small testis
- additional testicular condition affecting fertility
- bilateral palpable varicocele
- pathological sperm quality (in older adolescents)
- varicocele associated with a supranormal response to LHRH stimulation test
- symptomatic varicocele.

Repair of a large varicocele physically or psychologically causing discomfort may be also considered. Other varicoceles should be followed-up until a reliable sperm analysis can be performed (LE: 4; GR: C).

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9. MICROPENIS

9.1 Background

Micropenis is a small but otherwise normally formed penis with a stretched length of less than 2.5 SD below the mean (1-3).

Besides an idiopathic micropenis, two major causes of abnormal hormonal stimulation have been identified:

- Hypogonadotropic hypogonadism (due to an inadequate secretion of GnRH).
- Hypergonadotropic hypogonadism (due to failure of the testes to produce testosterone).

9.2 Diagnosis

The penis is measured on the dorsal aspect, while stretching the penis, from the pubic symphysis to the tip of the glans (1). The corpora cavernosa are palpated, the scrotum is often small, and the testes may be small and descended. Micropenis should be distinguished from buried and webbed penis, which is usually of normal size.

The initial evaluation has to define whether the aetiology of the micropenis is central (hypothalamic/pituitary) or testicular. A paediatric endocrinology work-up has to be carried out immediately. Karyotyping is mandatory in all patients with a micropenis.

Endocrine testicular function is assessed (baseline and stimulated testosterone, LH and FSH serum levels). Stimulated hormone levels may also give an idea of the growth potential of the penis. In patients with non-palpable testes and hypogonadotropic hypogonadism, laparoscopy should be carried out to confirm vanishing testes syndrome or intra-abdominal undescended hypoplastic testes. This investigation can be delayed until the age of 1 year (2).

9.3 Treatment

Pituitary or testicular insufficiency are treated by the paediatric endocrinologist. In patients with testicular failure and proven androgen sensitivity, androgen therapy is recommended during childhood and at puberty to stimulate the growth of the penis (LE: 2; GR: B) (4-7). In the presence of androgen insensitivity, good outcome of sexual function is questioned and gender conversion can be considered (8-10).

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10. DAYTIME LOWER URINARY TRACT CONDITIONS

10.1 Background

Following the new terminology document by the ICCS, 'daytime LUT conditions' is the new term used to group together functional incontinence problems in children (1). After any possible underlying uropathy or neuropathy has been excluded, a problem of incontinence in children is grouped into the category of 'daytime LUT conditions'. Night-time wetting is known as 'enuresis'.

Although exact data are unavailable, it is clear that the incidence of daytime LUT conditions is increasing. The changes in toilet training and toilet habits associated with a modern lifestyle have been blamed for the increase in incidence, but with little evidence. Rather, it is that modern life and higher hygiene standards have probably resulted in incontinence problems receiving more attention, so that an increase in prevalence could be probably be attributed to an increased awareness. There exists a wide variation in reported prevalence ranging from 2% to 20% (2-6). This wide variation might reflect the variation in definitions used.

10.2 Definition

Daytime LUT conditions are conditions that present with lower urinary tract symptoms (LUTS), including urge, incontinence, weak stream, hesitancy, frequency and urinary tract infections, but without overt uropathy or neuropathy.

Normal bladder storage and voiding involves low pressure and adequate bladder volume filling. This is followed by a continuous detrusor contraction, which results in complete bladder emptying, associated with an adequate relaxation of the sphincter complex. Normal urine storage by the bladder and evacuation

are controlled by a complex interaction between the spinal cord, brain stem, midbrain and higher cortical structures, associated with a complex integration of sympathetic, parasympathetic and somatic innervations (7).

It is understandable that this complex control mechanism is likely to be susceptible to developing different types of dysfunction. Various functional disorders of the detrusor-sphincter complex may occur during the sophisticated early development of normal mechanisms of micturition control. Voiding dysfunction is therefore thought to be the expression of incomplete or delayed maturation of the bladder sphincter complex.

Normal daytime control of bladder function matures between 2 and 3 years of age, while night-time control is normally achieved between 3 and 7 years of age (8). There are two main groups of voiding dysfunction, namely, filling-phase dysfunctions and voiding-phase dysfunctions.

10.2.1 Filling-phase dysfunctions

In filling-phase dysfunctions, the detrusor can be overactive, as in **overactive bladder (OAB) and urge syndrome**, or underactive, as in **underactive or highly compliant bladder** (formerly known as 'lazy bladder'). Some children habitually postpone micturition leading to **voiding postponement**.

10.2.2 Voiding-phase (emptying) dysfunctions

In voiding-phase (emptying) dysfunctions, interference with the sphincter and pelvic floor during detrusor contraction is the main dysfunction. The general term for this condition is **dysfunctional voiding**. Different degrees of dysfunction are described, depending on the strength of interference with the sphincter and pelvic floor. Weak interference results in staccato voiding, while stronger interference results in interrupted voiding and straining, due to an inability to relax during voiding.

Bladder sphincter dysfunction is often associated with bowel dysfunction such as obstipation and soiling. Sometimes, secondary anatomical changes are observed, such as trabeculation, diverticulae and vesicoureteral reflux.

10.3 Diagnosis

A non-invasive screening, consisting of history-taking, clinical examination, uroflow, ultrasound and voiding diary, is essential to reach a diagnosis.

In the paediatric age group, where the history is taken from both the parents and child together, a structured approach is recommended using a questionnaire. Many signs and symptoms related to voiding and wetting will be unknown to the parents and should be specifically requested, using the questionnaire as a checklist. A voiding diary is mandatory to determine the child's voiding frequency and voided volumes as well as the child's drinking habits. History-taking should also include assessment of bowel function. Some dysfunctional voiding scores have recently been developed and validated (9, 10).

Upon clinical examination, genital inspection and observation of the lumbosacral spine and the lower extremities is necessary to exclude obvious uropathy and neuropathy. Uroflow with post-void residual evaluates the emptying ability, while an upper urinary tract ultrasound screens for secondary anatomical changes. A voiding diary provides information about storage function and incontinence frequency, while a pad test can help to quantify the urine loss.

In the case of resistance to initial treatment, or in the case of former failed treatment, re-evaluation is warranted and further video-urodynamic studies may be considered. Sometimes, there are minor, underlying, urological or neurological problems, which can only be suspected using video-urodynamics.

In the case of anatomical problems, such as urethral valve problems, syringocoeles, congenital obstructive posterior urethral membrane (COPUM) or Moormann's ring, it may be necessary to perform further cystoscopy with treatment. If neuropathic disease is suspected, MRI of the lumbosacral spine and medulla can help to exclude tethered cord, lipoma or other rare conditions.

Psychological screening may be useful for children or families with major psychological problems associated with the voiding dysfunction.

10.4 Treatment

Treatment of voiding dysfunction consists of lower urinary tract rehabilitation, mostly referred to as urotherapy. Urotherapy means non-surgical, non-pharmacological, treatment of lower urinary tract (LUT) function. It is a very broad therapy field, incorporating many treatments used by urotherapists and other healthcare professionals (11). Urotherapy can be divided into standard therapy and specific interventions.

10.4.1 Standard therapy

Standard urotherapy is defined as non-surgical, non-pharmacological, treatment for LUT malfunction. It includes the following components:

- Information and demystification, which includes explanation about normal LUT function and how a

particular child deviates from normal function.

- Instruction about what to do about the problem, i.e. regular voiding habits, sound voiding posture, avoiding holding manoeuvres, etc.
- Lifestyle advice, regarding fluid intake, prevention of constipation, etc
- Registration of symptoms and voiding habits using bladder diaries or frequency-volume charts
- Support and encouragement via regular follow-up by the caregiver.

A success rate of 80% has been described for urotherapy programmes, independent of the components of the programme. However, the evidence level is low as most studies of urotherapy programmes are retrospective and non-controlled.

10.4.2 **Specific interventions**

As well as urotherapy, there are some specific interventions, including physiotherapy (e.g. pelvic floor exercises), biofeedback, alarm therapy and neurostimulation. Although good results with these treatment modalities have been reported, there have been no randomised controlled treatment trials (RCTs), so that the level of evidence is low (11-15).

In some cases, pharmacotherapy may be added. Antispasmodics and anticholinergics have been shown to be effective, though the level of evidence was low. More recently, a few RCTs have been published. One trial on tolterodine showed safety but not efficacy (16), while another RCT on propiverine showed both safety and efficacy (17) (LE: 1) (17). The difference in results is probably due to study design. Despite the low level of evidence for the use of anticholinergics and antimuscarinics, their use is recommended (GR: B) because of the large number of studies reporting a positive effect on OAB symptoms.

Although alpha-blocking agents are used occasionally, an RCT showed no benefit (18). Botulinum toxin injection seems promising, but can only be used off-label (19).

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11. MONOSYMPTOMATIC ENURESIS

11.1 Background

Enuresis is synonymous to intermittent nocturnal incontinence. It is a frequent symptom in children. With a prevalence of 5-10% at 7 years of age, it is one of the most prevalent conditions in childhood. With a spontaneous yearly cure rate of 15%, it is considered relatively benign (1,2).

However, 7 out of 100 children wetting the bed at age 7 will take this condition into adulthood. As it is a stressful condition, which puts a high psychological burden on children resulting in low self-esteem, treatment is advised from the age of 6-7 years onwards. Treatment is unnecessary in younger children in whom spontaneous cure is likely. The child's mental status, family expectations, social issues and cultural background need to be considered before treatment can be started.

11.2 Definition

Enuresis is the condition describing the symptom of incontinence during night. Any wetting during sleep above the age of 5 years is enuresis. However, most importantly, there is a single symptom only. Children with other LUT symptoms and enuresis are said to have **non-monosymptomatic enuresis**. Thorough history-taking, excluding any other daytime symptoms, is mandatory before diagnosing **monosymptomatic enuresis**. Any associated urinary tract symptoms make the condition a '**daytime LUT condition**' (3).

The condition is described as 'primary' when the symptom has always existed and the patient has not been dry for a period longer than 6 months. The condition is described as 'secondary', when there has been a symptom-free interval of 6 months. Genetically, enuresis is a complex and heterogeneous disorder. Loci have been described on chromosomes 12, 13 and 22 (3).

Three factors play an important pathophysiological role:

- high night-time urine output
- night-time low bladder capacity or increased detrusor activity
- arousal disorder.

Due to an imbalance between night-time urine output and night-time bladder capacity, the bladder can become easily full at night and the child will either wake up to empty the bladder or will void during sleep if there is a lack of arousal from sleep (1-3).

11.3 Diagnosis

The diagnosis is obtained by history-taking. In a patient with monosymptomatic enuresis, no further investigations are needed. A voiding diary, which records daytime bladder function and night-time urine output, will help to guide the treatment. An estimate of night-time urine production can be obtained by weighing diapers (nappies) in the morning and adding the volume of the morning void. Measuring the daytime bladder capacity gives an estimate of bladder capacity compared to normal values for age (4).

In most children, bedwetting is a familial problem, with most affected children found to have a history of bedwetting within the family.

11.4 Treatment

Before using alarm treatment or medication, simple therapeutic interventions should be considered.

11.4.1 Supportive treatment measures

Explaining the condition to the child and his parents helps to demystify the problem. Eating and drinking habits should be reviewed, stressing normal fluid intake during day and reducing fluid intake in the hours before sleep. Keeping a chart depicting wet and dry nights has been shown to be successful.

Counselling, provision of information, positive reinforcement and increasing (and supporting) motivation of the child should be introduced first. There is a high level of evidence showing that supportive treatment is more successful than doing nothing, though the cure rate is not significantly high. However, supportive therapy as an initial management carries a high grade of recommendation (4).

If supportive measures have no success, further treatment modalities must be considered, of which pharmacological treatment and alarm treatment are the two most important.

11.4.2 Alarm treatment

Alarm treatment is the best form of treatment for arousal disorder (LE: 1) (GR: A). Initial success rates of 80% with low relapse rates are realistic, especially when night-time diuresis is not too high and bladder capacity is not too low (5).

11.4.3 Medication

In the case of high night-time diuresis, success rates of 70% can be obtained with desmopressin (DDAVP), either as tablets, 200-400 µg or as sublingual desmopressin oral lyophilisate, 120-240 µg. A nasal spray is no longer recommended due to an increased risk of overdosing (6) (LE: 1) (GR: A) (7). However, relapse rates are high after DDAVP discontinuation (4).

In the case of a small bladder capacity, treatments with antispasmodics or anticholinergics are possible (4). However, when these medications are necessary, the condition is no longer considered to be monosymptomatic.

Imipramine, which has been popular in the treatment of enuresis, achieves only a moderate response rate of 50% and has a high relapse rate. Furthermore, cardiotoxicity and death with overdose are described. Its use should therefore be discouraged (LE: 1) (GR: C) (8).

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12. MANAGEMENT OF NEUROGENIC BLADDER IN CHILDREN

12.1 Background

Neurogenic detrusor-sphincter dysfunction (NDSD) can develop as a result of a lesion at any level in the nervous system. This condition contributes to various forms of lower urinary tract dysfunction, which may lead to incontinence, urinary tract infections (UTIs), vesicoureteral reflux (VUR), and renal scarring. Surgery may be required to establish adequate bladder drainage. If not managed properly, NDSD can potentially cause renal failure, requiring dialysis or transplantation.

The management of neurogenic bladder sphincter dysfunction in children has undergone major changes over the years. Although nappies (diapers), permanent catheters, external appliances, Crede's manoeuvre and various forms of urinary diversion have been acceptable treatment methods, these are now reserved for only a small number of resistant patients. The introduction of clean intermittent catheterisation (IC) has revolutionised the management of children with neurogenic bladder. Not only has it made conservative management a very successful treatment option, but it has also made surgical creation of continent reservoirs a very effective treatment alternative, with a good outcome for quality of life and kidney protection (1-3).

Neurogenic bladder in children with myelodysplasia presents with various patterns of detrusor-sphincter dysfunction within a wide range of severity. About 15% of neonates with myelodysplasia have no signs of neurourological dysfunction at birth. However, there is a high chance of progressive changes in the dynamics of neurological lesions with time. Even babies with normal neurourological function at birth have a one in three risk of developing either detrusor sphincter dyssynergia or denervation by the time they reach puberty. At birth, the majority of patients have normal upper urinary tracts, but nearly 60% of them develop upper tract deterioration due to infections, bladder changes and reflux (4-7).

As our understanding of urodynamic studies has evolved, it has allowed us to understand the nature and severity of problems and manage these patients in a more rational and individualised manner. Despite the remarkable changes of the last quarter of the 20th century, the main goals of treatment have remained the same, i.e. prevention of urinary tract deterioration and achievement of continence at an appropriate age.

12.2 Definition

The most common presentation is at birth with myelodysplasia. The term myelodysplasia includes a group of developmental anomalies that result from defects in neural tube closure. Lesions may include spina bifida occulta, meningocele, lipomyelomeningocele, or myelomeningocele. Myelomeningocele is by far the most common defect seen and the most detrimental. Traumatic and neoplastic spinal lesions of the cord are less frequent in children. Additionally, different growth rates between the vertebral bodies and the elongating spinal cord can introduce a dynamic factor to the lesion. Scar tissue surrounding the cord at the site of meningocele closure can tether the cord during growth.

In occult myelodysplasia, the lesions are not overt and often occur with no obvious signs of neurological lesion. In nearly 90% of patients, however, a cutaneous abnormality overlies the lower spine, and this condition can easily be detected by simple inspection of the lower back (8).

Total or partial sacral agenesis is a rare congenital anomaly that involves absence of part or all of one or more sacral vertebrae. This anomaly can be part of the caudal regression syndrome, and must be considered in any child presenting with anorectal malformation (ARM). Patients with cerebral palsy may also present with varying degrees of voiding dysfunction, usually in the form of uninhibited bladder contractions (often due to spasticity of the pelvic floor and sphincter complex) and wetting.

Bladder sphincter dysfunction is poorly correlated with the type and spinal level of the neurological lesion.

12.3 Classification

The purpose of any classification system is to facilitate the understanding and management of the underlying

pathology. There are various systems of classification of neurogenic bladder.

Most systems of classification were formulated primarily to describe those types of dysfunction secondary to neurological disease or injury. Such systems are based on the localisation of the neurological lesion and the findings of the neurourological examination. These classifications have been of more value in adults, in whom neurogenic lesions are usually due to trauma and are more readily identifiable.

In children, the spinal level and extent of congenital lesion are poorly correlated with the clinical outcome. Urodynamic and functional classifications have therefore been more practical for defining the extent of the pathology and planning treatment in children.

The bladder and sphincter are two units working in harmony to make a single functional unit. The initial approach should be to evaluate the state of each unit and define the pattern of bladder dysfunction. According to the nature of the neurological deficit, the bladder and sphincter may be in either an overactive or inactive state:

- the bladder may be overactive with increased contractions, and low capacity and compliance, or inactive with no effective contractions
- the outlet (urethra and sphincter) may be independently overactive causing functional obstruction, or paralysed with no resistance to urinary flow
- these conditions may present in different combinations.

This is mainly a classification based on urodynamic findings. The understanding of the pathophysiology of disorders is essential to plan a rational treatment plan for each individual patient. In meningocele, most patients will present with hyper-reflexive detrusor and dyssynergic sphincter, which is a dangerous combination as pressure is built up and the upper tract is threatened.

12.4 Urodynamic studies

Urodynamic studies enable the clinician to observe lower urinary tract function and its deviations from normal. Since the treatment plan mainly depends upon a good understanding of the underlying problem in the lower urinary tract, a well-performed urodynamic study is mandatory in the evaluation of each child with neurogenic bladder.

As the bony level often does not correspond with the neurological defect present, and as the effect of the lesion on bladder function cannot be entirely determined by radiographic studies or physical examination, the information gained from a urodynamic study is priceless. A urodynamic study also provides the clinician with information about the response of the vesicourethral unit to therapy, as demonstrated by improvement or deterioration in follow-up.

It is important to determine several urodynamic parameters, including:

- the bladder capacity;
- the intravesical filling pressure;
- the intravesical pressure at the moment of urethral leakage;
- the presence or absence of reflex detrusor activity;
- the competence of the internal and external sphincteric mechanisms;
- the degree of coordination of the detrusor and sphincteric mechanisms;
- the voiding pattern;
- the post-voiding residual urine volume.

12.4.1 Method of urodynamic study

There is very little comparative data evaluating the complexity and invasiveness of urodynamic testing for neurogenic bladders in children.

12.4.2 Uroflowmetry

As uroflowmetry is the least invasive of all urodynamic tests, it can be used as an initial screening tool. It provides an objective way of assessing the efficiency of voiding, and, together with an ultrasonographic examination, the residual urine volume can also be determined. Unlike in children with non-neurogenic voiding dysfunction, uroflowmetry will rarely be used as a single investigational tool in children with neurogenic bladders, as it does not provide information for bladder storage, yet it may be very practical to monitor emptying in the follow-up. The main limitation of a urodynamic study is the need for the child to be old enough to follow instructions and void on request.

The recording of pelvic floor or abdominal skeletal muscle activity by electromyography (EMG) during uroflowmetry can be used to evaluate coordination between detrusor and the sphincter. As it is a non-invasive test, combined uroflowmetry and EMG may be very useful in evaluating sphincter activity during voiding (9-12) (LE: 3; GR: C).

12.4.3 **Cystometry**

Although moderately invasive and dependent on a cooperative child, cystometry in children provides valuable information regarding detrusor contractility and compliance. The amount of information obtained from each study is related to the degree of interest and care given to the test.

It is important to be aware of the alterations in filling and emptying detrusor pressures as the infusion rates change during cystometry. Slow fill cystometry (filling rate < 10 mL/min) is recommended by the International Children's Continence Society (ICCS) for use in children (13). However, it has been suggested that the infusion rate should be set according to the child's predicted capacity, based on age and divided by 10 (14).

Several clinical studies using conventional artificial fill cystometry to evaluate neurogenic bladder in children have reported that conventional cystometry provides useful information for diagnosis and follow-up of children with neurogenic bladder (15-20). All the studies were retrospective clinical series and lacked comparison with natural fill cystometry, so that the grade of recommendation for an artificial cystometry in children with neurogenic bladder is not high (LE: 4). Additionally, there is evidence suggesting that natural bladder behaviour is altered during regular artificial filling cystometry (21,22).

However, conventional cystometry in infants is useful for predicting future deterioration. Urodynamic parameters, such as low capacity and compliance and high leak-point pressures, are poor prognostic factors for future deterioration. Resolution of reflux is less likely to happen in such bladders (15,20,22) (LE: 4).

During natural fill cystometry, the bladder is allowed to fill naturally and the bladder and abdominal pressures are recorded using microtransducer catheters. Theoretically, this allows investigation of bladder function in near-physiological conditions. Studies on natural fill cystometry in children report similar results to those of studies done in adults. Natural fill cystometry gives a lower detrusor pressure rise during filling, and lower voided volumes with higher voiding pressures. The incidence of bladder overactivity is higher with natural filling cystometry when compared with conventional artificial filling cystometry (21,23,24).

Although there are only a few studies on natural fill cystometry in children with neurogenic bladder, the results suggest that natural fill cystometry detects new findings compared with diagnoses delivered by conventional cystometry (21) (LE: 3). However, the comparison between natural fill and artificial fill cystometry has not been performed against a gold standard, making it difficult to conclude which study is a true reflection of natural bladder behaviour. Findings in the non-neurogenic adult population have questioned the reliability of natural fill cystometry, as natural fill cystometry has shown a high incidence of bladder overactivity in totally normal asymptomatic volunteers (25).

The main disadvantage of natural fill cystometry is that it is labour-intensive and time-consuming. Moreover, because of the transurethral catheter used during this study, false-positive findings caused by the catheter are possible. Especially in children, the recording of events is difficult and there is an increased risk of artefacts, which makes interpretation of the huge amount of data even more difficult.

Natural fill cystometry remains a new technique in the paediatric population. More data need to be gathered in a standard way before it can be widely accepted (11).

12.5 **Management**

The medical care of children with myelodysplasia with a neurogenic bladder requires constant observation and adaptation to new problems. In the first years of life, the kidneys are highly susceptible to back-pressure and infection. During this period, the emphasis is on documenting the pattern of NDSD, and assessing the potential for functional obstruction and VUR.

12.5.1 **Investigations**

An abdominal ultrasound obtained as soon as possible after birth will detect hydronephrosis or other upper genitourinary tract pathology. Following ultrasound, a voiding cystourethrogram should be obtained to evaluate the lower urinary tract. Measurement of residual urine during both ultrasound and cystography should also be done. These studies provide a baseline for the appearance of the upper and lower urinary tracts, can facilitate the diagnosis of hydronephrosis or VUR, and can help identify children at risk for upper genitourinary tract deterioration and impairment of renal function.

A urodynamic evaluation can be done after some weeks, and needs to be repeated at regular intervals, in combination with evaluation of the upper tracts (26-28) (LE: 3; GR: B).

12.5.2 **Early management with intermittent catheterisation**

Overwhelming experience gained over the years with early management of neurogenic bladder in infants has led to a consensus that children do not have upper tract deterioration when managed early with IC and anticholinergic medication. IC should be started soon after birth in all babies, especially in those with signs of possible outlet obstruction (26,29-37) (LE: 2; GR: B).

The early initiation of IC in the newborn period makes it easier for parents to master the procedure and for children to accept it as they grow older (38,39).

Early management results in fewer upper tract changes, but also better bladder protection and lower incontinence rates. It has been suggested that increased bladder pressures due to detrusor sphincter dyssynergia cause secondary changes of the bladder wall. These fibroproliferative changes in the bladder wall may cause further loss of elasticity and compliance, resulting in a small non-compliant bladder with progressively elevated pressures.

Early institution of IC and anticholinergic drugs may prevent this in some patients (2,37,40) (LE: 3). The retrospective evaluation of patients has also shown that significantly fewer augmentations were required in patients with an early start of IC (33,34) (LE: 4).

12.5.3 Medical therapy

At present, oxybutynin, tolterodine, trospium and propiverine are the most frequently used drugs, with oxybutynin being the most studied.

Two different forms of tolterodine have been investigated in children with neurogenic bladder. The extended release formulation of tolterodine has been found to be as efficient as the instant release form, with the advantages of being single dosage and less expensive. Although the clinical outcome is encouraging, the level of evidence is low for anticholinergic medication because there are no controlled studies (40,41-47) (LE: 3; GR: B).

The use of medication to facilitate emptying in children with neurogenic bladder has not been well studied in the literature. A few studies investigating the use of α -adrenergic blockade in children with neurogenic bladder have reported a good response rate, but the studies lacked controls, and long-term follow-up is warranted (48) (LE: 4; GR: C).

12.5.3.1 Botulinum toxin injections

In neurogenic bladders that are refractory to anticholinergics and remain in a small-capacity, high-pressure state, a novel treatment alternative is the injection of botulinum toxin into the detrusor. Initial promising results in adults have initiated its use in children. So far, studies of the clinical effect of botulinum toxin in children have been open trials, and there is a lack of prospective controlled trials. However, the injection of botulinum toxin in therapy-resistant bladders appears to be an effective and safe treatment alternative.

This treatment seems to be more effective in bladders with evidenced detrusor overactivity, while non-compliant bladders without obvious detrusor contractions are unlikely to respond to this treatment (49-52).

The dosage in children should be determined by body weight and minimum age, with caution with regard to total dose if it is also being used to treat spasticity. Currently, it is unclear how many times this treatment can be repeated, although repetitive treatment has been found to be safe in adults (53-55) (LE: 3; GR: C).

In a single study, urethral sphincter botulinum-A toxin injection has been shown to be effective in decreasing urethral resistance and improve voiding. The evidence is still too low to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases (56).

12.5.4 Management of bowel incontinence

Children with neurogenic bladder have disturbances of bowel function as well as urinary function. Bowel incontinence in these children is frequently unpredictable. It is related to the turnover rate of faecal material in the anal area after evacuation, the degree of intactness of sacral cord sensation and motor function, and reflex reactivity of the external anal sphincter (57).

Bowel incontinence is managed most commonly with mild laxatives, such as mineral oil, combined with enemas to facilitate removal of bowel contents. A regular and efficient bowel emptying regimen is often necessary to maintain faecal continence, and may have to be started at a very young age. With antegrade or retrograde enemas, most of these children will have decreased constipation problems and may attain some degree of faecal continence (58-62) (LE: 3).

Biofeedback training programmes to strengthen the external anal sphincter have not been shown to be more effective than a conventional bowel management programme in achieving faecal continence (63). Electrostimulation of the bowel may also offer a variable improvement in some patients (64) (LE: 3; GR: C).

12.5.5 Urinary tract infection

UTIs are common in children with neurogenic bladders. In the absence of reflux, UTIs should be treated symptomatically. There is strong evidence for not prescribing antibiotics to patients who have bacteriuria but no clinical symptoms. Although bacteriuria is seen in more than half of children on clean IC, patients who are asymptomatic do not need treatment (65-67) (LE: 3). Patients with VUR should usually be placed on prophylactic antibiotics to reduce the incidence of pyelonephritis, which can potentially lead to renal damage (68, 69).

12.5.6 Sexuality

Sexuality, while not an issue in childhood, becomes progressively more important as the patient gets older. This issue has historically been overlooked in individuals with myelodysplasia. However, patients with myelodysplasia do have sexual encounters. Studies indicate that at least 15-20% of males are capable of fathering children and 70% of females can conceive and carry a pregnancy to term. It is therefore important to counsel patients about sexual development in early adolescence.

12.5.7 Bladder augmentation

Children with a good response to anticholinergic treatment and an overactive sphincter may be continent between catheterisations. Bladder pressure and development of the upper urinary tract will determine whether additional treatment is necessary.

Therapy-resistant overactivity of the detrusor, or small capacity and poor compliance, will usually need to be treated by bladder augmentation. A simple bladder augmentation using intestine may be carried out if there is any bladder tissue, a competent sphincter and/or bladder neck, and a urethra that can be catheterised. Stomach is rarely used as an augmenting patch because of the associated complications (70). Ileal or colonic patches are frequently used for augmenting the bladder, with either intestinal segment appearing to be equally useful. Despite some advantages (e.g. avoiding mucus, decreased malignancy rate and fewer complications), alternative urothelium-preserving techniques, such as autoaugmentation and seromuscular cystoplasty, have not proven to be as successful as standard augmentation with intestine (71,72).

A range of applications of engineered bladder tissues are at different stages of development. There have been a few in pre-clinical trials; recent progress suggests that engineered bladder tissues may have an expanded clinical application in the future (73).

12.5.8 Bladder outlet procedures

Children with detrusor overactivity, but with underactive sphincters, will be better for protecting their upper tracts, although they will be severely incontinent. Initial treatment is IC (as it might reduce the degree of incontinence and offers much better control over UTIs) with anticholinergic drugs. At a later age, the outlet resistance will be increased in order to render them continent. No medical treatment available has been validated to increase bladder outlet resistance. Alpha-receptor stimulation of the bladder neck has not been very effective (74-79).

When conservative measures fail, surgical procedures need to be considered for maintaining continence. Although a simple augmentation is sufficient for most low-capacity, high-pressure bladders, augmentation with additional bladder outlet procedures is required when both the bladder and outlet are deficient. Bladder outlet procedures include bladder neck reconstruction or other forms of urethral reconstruction.

Various procedures can be used on the bladder neck to increase resistance, but all of them may complicate transurethral catheterisation. Augmentation with surgical closure of the bladder neck may be required primarily, or as a secondary procedure in certain rare clinical situations. In this situation, a continent stoma will be required. However, most surgeons prefer to leave the bladder neck and urethra patent as a safety precaution.

12.5.9 Continent stoma

Augmentation with an additional continent stoma is utilised primarily after failure of previous bladder outlet surgery. It is also advisable when an inability to catheterise transurethrally is likely. An abdominal wall continent stoma may be particularly beneficial to wheelchair-bound spina bifida patients, who often have difficulty with urethral catheterisation or are dependent on others to catheterise the bladder. For continence with augmentation and an abdominal wall stoma, an adequate bladder outlet mechanism is essential to maintain continence.

12.5.10 Total bladder replacement

Total bladder replacement in anticipation of normal voiding in children is very rare, as there are infrequent indications for a total cystectomy, with preservation of the bladder outlet and a competent urethral sphincter. This type of bladder replacement is much more common in adult urological reconstruction. Any type of major bladder and bladder outlet construction should be performed in centres with sufficient experience of the surgical technique, and with experienced healthcare personnel to carry out post-operative follow-up (80-82).

12.5.11 Lifelong follow-up of neurogenic bladder patients

Neurogenic bladder patients require lifelong supervision, and the monitoring of renal function is extremely important. Periodic investigation of upper tract changes, renal function and bladder status is mandatory. Repeat urodynamic tests are therefore needed more frequently (every year) in younger children and less

frequently in older children. From the urological viewpoint, a repeat urodynamic study is warranted when the patient has a change in symptoms or undergoes any neurosurgical procedure. In the case of any apparent changes in the upper and lower urinary tract, or changes in neurological symptoms, a more detailed examination including urodynamics and spinal magnetic resonance imaging is indicated.

Renal failure can progress slowly or occur with startling speed in these children. Patients who have undergone reconstructive procedures using intestine should be regularly followed-up for complications such as infection, stone formation, reservoir rupture, metabolic changes, and malignancy (83).

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13. DILATATION OF THE UPPER URINARY TRACT (URETEROPELVIC JUNCTION AND URETEROVESICAL JUNCTION OBSTRUCTION)

13.1 Background

Dilatation of the upper urinary tract still presents a significant clinical challenge in determining which patient may gain benefit by therapy.

Ureteropelvic junction (UPJ) obstruction is defined as impaired urine flow from the pelvis into the proximal ureter with subsequent dilatation of the collecting system and the potential to damage the kidney. It is the most common cause of neonatal hydronephrosis (1). It has an overall incidence of 1:1500 and a ratio of males to females of 2:1 in newborns.

Ureterovesical junction (UVJ) obstruction is an obstructive condition of the distal ureter as it enters the bladder, commonly called a primary obstructive megaureter. Megaureters are ranked as second in the differential diagnosis of neonatal hydronephrosis. They occur more often in males and are more likely to occur on the left side (2).

Much more difficult is the definition of obstruction. Creating a divide between 'obstructed' and 'non-obstructed' urinary tracts, as if entities could be as clearly differentiated as 'black' and 'white', is impossible. Currently, the most popular definition is that obstruction represents any restriction to urinary outflow that, if left untreated, will cause progressive renal deterioration (3).

13.2 Diagnosis

Due to the widespread use of ultrasonography during pregnancy, antenatal hydronephrosis is being detected with increasing frequency (4). The challenge in the management of dilated upper urinary tracts is to decide which child can be observed, which one should be managed medically, and which one requires surgical intervention. There is no single definitive test able to distinguish obstructive from non-obstructive cases (Figure 2).

13.2.1 Antenatal ultrasound

Usually between the 16th and 18th weeks of pregnancy, the kidneys are visualised routinely, when almost all amniotic fluid consists of urine. The most sensitive time for fetal urinary tract evaluation is the 28th week. If dilatation is detected, ultrasound should focus on the laterality, severity of dilatation, and echogenicity of the kidneys, hydronephrosis or hydro-ureteronephrosis, bladder volume and bladder emptying, sex of the child, and amniotic fluid volume, respectively (5).

13.2.2 Postnatal ultrasound

Since transitory neonatal dehydration lasts about 48 hours, imaging should be performed after this period of postnatal oliguria. In severe cases (bilateral dilatation, solitary kidney, oligohydramnios), immediate postnatal sonography is recommended (6). During ultrasound examination, the anteroposterior diameter of the renal pelvis, calyceal dilatation, kidney size, thickness of the parenchyma, cortical echogenicity, ureters, bladder wall and residual urine are assessed.

13.2.3 Voiding cystourethrogram (VCUG)

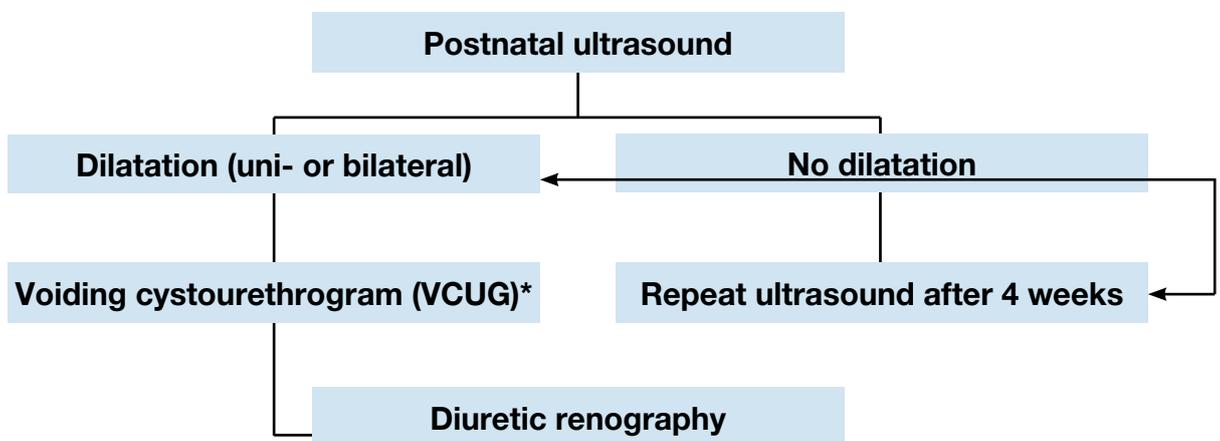
In newborns with identified upper urinary tract dilatation, the presence of primary or important associated factors that must be detected include vesicoureteral reflux in up to 25% of affected children (15), urethral valves, ureteroceles, diverticula and neurogenic bladder. Conventional VCUG is the method of choice for primary diagnostic procedures (7).

13.2.4 Diuretic renography

Diuretic renography is the most commonly used diagnostic tool to detect the severity and functional significance of urine transport problems. ^{99m}Tc -MAG3 is the radionuclide of choice. It is important to perform the study under standardised circumstances (hydration, transurethral catheter) between the fourth and sixth weeks of life (8).

Oral fluid intake is encouraged prior to examination. Fifteen minutes before injection of the radionuclide, it is mandatory to give normal saline intravenous infusion at a rate of 15 ml/kg over 30 minutes and then at a maintenance rate of 4 ml/kg/hour throughout the whole time of the investigation (9). The recommended dose of furosemide is 1 mg/kg for infants during the first year of life, while 0.5 mg/kg should be given to children aged 1 to 16 years up to a maximum dose of 40 mg.

Figure 2: Diagnostic algorithm for dilatation of the upper urinary tract



* A diagnostic work-up including VCUG has to be discussed with the parents since a possibly detected reflux might have absolutely no clinical impact. On the other hand, a reflux rate of up to 25% in cases of prenatally detected and postnatally confirmed hydronephrosis is reported in the literature (15) and might therefore have some forensic impact as well.

13.3 Treatment

13.3.1 Prenatal management

Counselling the parents is one of the most important aspects of care. The prognosis for an hydronephrotic kidney, even if severely affected, is hopeful. An hydronephrotic kidney may still be capable of providing meaningful renal function, whereas a severely hypoplastic and dysplastic kidney has a hopeless outlook. It is important to explain to the parents the timing and accuracy of establishing the definitive diagnosis for their child. In some cases, there is an obvious indication of severity, including massive bilateral dilatation, bilateral evidence of hypoplastic dysplasia, progressive bilateral dilatation with oligohydramnios, and pulmonary hypoplasia.

Intrauterine intervention is rarely indicated and should only be performed in well-experienced centres (10).

13.3.2 UPJ obstruction

It is most important to make the decision on the basis of serial investigations, applying the same technique and performed by the same institution under standardised circumstances. Symptomatic obstruction (recurrent flank pain, urinary tract infection) requires surgical correction using a pyeloplasty, according to the standardised open technique of Hynes and Anderson (11). Recently, increasingly more data have become available supporting the use of a laparoscopic or retroperitoneoscopic approach to achieve a dismembered pyeloplasty. In addition, laparoscopic suturing has been improved by the use of robotics (16). However, these methods lack very long-term data and will require time to be fully proven. In asymptomatic cases, conservative follow-up can be the treatment of choice.

Indications for surgical intervention are an impaired split renal function (< 40%), a decrease of split renal function of more than 10% in subsequent studies, increased anteroposterior diameter on the ultrasound, and grade III and IV dilatation as defined by the Society for Fetal Urology.

13.4 Megaureter

Concerning the treatment options of secondary megaureters (see Chapter 14, *vesicoureteric reflux*).

If a functional study reveals and confirms adequate ureteral drainage, conservative management is the best option. Initially, low-dose prophylactic antibiotics within the first year of life are recommended for prevention of urinary tract infections, although there are no prospective randomised trials to evaluate this regimen (12).

With spontaneous remission rates of up to 85% in primary megaureter cases, surgical management is no longer recommended, except for megaureters with recurrent urinary tract infections, deterioration of split renal function and significant obstruction (13).

The initial approach to the ureter can be either intravesical, extravesical, or combined. Straightening the ureter is necessary without devascularisation. Ureteral tapering should enhance urinary flow into the bladder. The ureter must be tapered to achieve a diameter for an antireflux repair. There are several tailoring techniques, e.g. ureteral imbrication or excisional tapering (14).

13.5 Conclusion

With the use of routine perinatal sonography, hydronephrosis caused by UPJ or UVJ obstruction is now increasingly recognised. Meticulous and repeat postnatal evaluation is mandatory to try to identify any obstructive cases at risk of renal deterioration and requiring surgical reconstruction. Surgical methods are fairly standardised and have a good clinical outcome.

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14. VESICoureTERIC REFLUX IN CHILDREN

14.1 Background

Vesicoureteral reflux (VUR), or the retrograde flow of urine from the bladder into the ureter, is an anatomical and/or functional disorder with potentially serious consequences, such as renal scarring, hypertension and renal failure. Fortunately, patients with VUR present within a wide range of severity, and a good proportion of reflux patients will not develop renal scars and probably will not need any intervention(1).

Vesicoureteric reflux is a very common urological anomaly in children, with an incidence of nearly 1%. Its management is one of the most controversial issues in paediatric urology.

The main goal in management is the preservation of kidney function. By defining and analyzing the risk factors for each patient (i.e. age, gender, reflux grade, lower urinary tract dysfunction (LUTD), anatomical abnormalities and kidney status), it is possible to identify those patients with a potential risk of urinary tract infections (UTIs) and renal scarring.

Controversy persists over the optimal management of VUR, particularly the choice of diagnostic procedures, treatment (medical, endoscopic or open surgical), and the timing of treatment.

Because many children are asymptomatic and invasive diagnostic procedures are performed only when clinically indicated, it is difficult to give an exact prevalence of VUR. However, the prevalence of VUR in normal children has been estimated to be 0.4-1.8% (2).

Among infants prenatally identified with hydronephrosis on ultrasonography (US), who were screened for VUR, the prevalence of VUR was 16.2 % (7-35%) (3). Siblings of children with VUR have a 27.4 % (3-51%) risk of also having VUR, while the offspring of parents with VUR have a higher incidence of 35.7% (21.2-61.4%) (3). However, the offspring and siblings present with lower grades of reflux. When VUR is discovered in symptomatic siblings, it is usually high grade and associated with a high incidence of reflux nephropathy. Even when asymptomatic, siblings and offspring of those with VUR may be diagnosed with high-grade reflux and scarring.

The incidence of VUR is much higher among children with urinary tract infections (UTIs) (30-50%, depending on age). Urinary tract infections are more common in females than boys due to anatomical differences. However, among all children with UTIs, boys are more likely to have VUR than girls (29% of male vs 14% of females). Boys also tend to have higher grades of VUR diagnosed at younger ages, though their VUR is more likely to resolve (4-7).

There is a clear co-prevalence between LUTD and VUR, although the pathophysiological relationship between LUTD and VUR has not yet been resolved (8). Some studies have described a prevalence of 40-60% VUR in children with LUTD (9). Despite the evidence of an increased prevalence of VUR in LUTD, there is no

research to suggest the best way of addressing the situation. It is possible that VUR is secondary to LUTD, and that treatment of LUTD will therefore result in correction of VUR. On the other hand, high-grade VUR may affect bladder dynamics, which subsequently leads to LUTD.

A recently published Swedish reflux trial demonstrated bladder dysfunction in 34% of patients, of whom 9% had isolated overactive bladder and 24% had voiding phase dysfunction. There was a significant negative correlation between dysfunction at 2 years and improved dilating reflux. Renal damage at study entry and follow-up was associated with LUTD at 2 years. Recurrent UTIs were seen in 33% of children with, and in 20% without, bladder dysfunction (10).

The spontaneous resolution of VUR is dependent on age at presentation, gender, grade, laterality, mode of clinical presentation and anatomy (11). Faster resolution of VUR is more likely with age < 1 year at presentation, lower grade of reflux (grade 1-3) and asymptomatic presentation with prenatal hydronephrosis or sibling reflux. The overall resolution rate is high in congenital high-grade VUR during the first years of life. The presence of diffuse scarring, major renal abnormality, bladder dysfunction and breakthrough febrile UTIs are negative predictive factors for reflux resolution (12-14).

Vesicoureteral reflux may result in significant morbidity from acute renal infections and from renal scarring. Unless properly treated, recurrent UTIs may have a negative impact on somatic growth and the general well being of children with VUR. About 10-40% of children with symptomatic VUR have evidence of renal scarring, resulting from either congenital dysplasia and/or acquired post-infectious damage (15-17). Higher grades of VUR present with higher rates of renal scars. Scar rates vary in different patient groups. In the prenatal hydronephrosis group, renal scarring occurs in about 10% of patients (18-23), whereas in patients with LUTD, it can be up to 30% (24-26). Scarring in the kidney may inversely affect renal growth and function, with bilateral scarring increasing the risk of renal insufficiency. Reflux nephropathy (RN) may be the most common cause of childhood hypertension. Follow-up studies show that about 10-20% of children with RN develop hypertension or end-stage renal disease (27).

14.2 Diagnostic work-up

The diagnostic work-up should aim to evaluate the overall health and development of the child, the presence of UTIs, renal status, the presence of VUR and lower urinary tract function.

A basic diagnostic work-up comprises a detailed medical history (including family history, screening for LUTD), physical examination including blood pressure measurement, urinalysis (including proteinuria), and urine culture.

Imaging is the basis of diagnosis and management of VUR. The standard imaging tests include renal and bladder ultrasonography (US), voiding cystourethrography (VCUG) and nuclear renal scans. The criterion standard in diagnosis of VUR is VCUG, especially at the initial work-up. This test provides precise anatomical detail and allows grading of the VUR (28). In 1985, the International Reflux Study Committee introduced a uniform system for the classification of VUR (29,30) (Table 1). The grading system combines two earlier classifications and is based upon the extent of retrograde filling and dilatation of the ureter, the renal pelvis and the calyces on a VCUG (31).

Radionuclide studies for detection of reflux have lower radiation exposure than VCUG, but the anatomical details depicted are inferior (32). Recent studies on alternative imaging modalities for detection on VUR have yielded good results with voiding urosonography and magnetic resonance VCUG (33-35). However, despite the concerns about ionising radiation (although very much reduced due to digital picture processing) and its invasive nature, conventional VCUG still remains the gold standard because it allows a better determination of the grade of VUR (in a single or duplicated kidney) and assessment of the bladder and urethral configuration.

Table 1: Grading system for VUR on voiding cystourethrography, according to the International Reflux Study Committee (29)

Grade I	Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation
Grade II	Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices
Grade III	Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices
Grade IV	Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible
Grade V	Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

^{99m}Tc-Dimercaptosuccinic acid (DMSA) is the best nuclear agent for visualising the cortical tissue and differential function between both kidneys. DMSA is taken up by proximal renal tubular cells and is a good indicator of functioning renal parenchyma. In areas of acute inflammation or scarring, DMSA uptake will be poor and appear as cold spots. DMSA scans are therefore used to detect and monitor renal scarring. A baseline DMSA scan at the time of diagnosis can be used for comparison with successive scans later during follow-up (31,36). DMSA can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis (37). Children with a normal DMSA scan during an acute UTI have a low risk of renal damage (38).

Video-urodynamic studies are only important in patients in whom secondary reflux is suspected, such as patients with spina bifida or boys whose VCUG is suggestive of posterior urethral valves. In the case of lower urinary tract symptoms (LUTS), diagnosis and follow-up can be limited to non-invasive tests (voiding charts, US, uroflowmetry) (8).

Except for assessment and treatment of infravesical pathology, cystoscopy may only be performed at the time of surgery to identify additional anatomical abnormalities, such as ureteral duplication and ureteral ectopia.

The choice of imaging modalities varies depending on the mode of presentation.

14.2.1 Infants presenting because of prenatally diagnosed hydronephrosis

Ultrasonography of the kidney and bladder is the first standard evaluation tool for children with prenatally diagnosed hydronephrosis. It is non-invasive and provides reliable information regarding kidney structure, size, parenchymal thickness, collecting system dilatation and ureteric dilatation and bladder abnormalities. (39,40).

Ultrasonography should be delayed to the end of first week after birth because of early oliguria in the neonate. It is essential to evaluate the bladder, as well as the kidneys. The degree of dilatation in the collecting system under US, when the bladder is both full and empty may provide significant information in regard to the presence of VUR. Bladder wall thickness and configuration may be an indirect sign of LUTD and reflux. The absence of hydronephrosis on ultrasound after birth excludes the presence of significant obstruction; however, it does not exclude VUR.

Monitoring with careful US avoids unnecessary invasive and irradiating examinations. The first two US scans within the first 1-2 months of life are highly accurate for defining the presence or absence of renal pathology. In infants with two, normal, postnatal, successive US, VUR is a rare entity, and if present it is likely to be low grade (19,41).

The degree of hydronephrosis is not a reliable indicator for the presence of VUR, even though cortical abnormalities are more common in high-grade hydronephrosis (3). The presence of cortical abnormalities on US (defined as cortical thinning and irregularity, as well as increased echogenicity) warrants the use of VCUG for detecting VUR (3). DMSA provides more reliable and quantitative measurement of the degree of cortical abnormalities when first detected with US.

The use of VCUG is recommended in patients with US findings of bilateral high-grade hydronephrosis, duplex kidneys, ureterocele, ureteric dilatation and abnormal bladders, as the likelihood of VUR is much higher. In all other conditions, the use of VCUG to detect reflux is optional (3,42-44). When cases depicted by prenatal US become symptomatic with UTIs, further evaluation with VCUG should be considered (44).

Patients with severe hydronephrosis and patients whose hydronephrosis sustains or progresses, need further evaluation to exclude obstruction (see Chapter 13).

14.2.2 Siblings and offspring of reflux patients

The screening of asymptomatic siblings and offspring is very controversial. Some authors think that early identification of children with VUR may prevent episodes of UTI and renal scarring, while others think that

screening asymptomatic individuals is likely to result in significant over-treatment of clinically insignificant VUR.

The overall estimate for renal cortical abnormalities is 19.3% (range, 11-54%), with 27.8% having renal damage in cohorts of symptomatic and asymptomatic children combined. In asymptomatic siblings only, the rate of renal damage is 14.4% (range 0-100%). Early screening appears to be more effective than late screening in preventing further renal damage (3,45,46).

The lack of randomised clinical trials for screened patients to assess clinical health outcomes makes evidence-based guideline recommendations difficult.

Recommendations for paediatric screening for VUR

- The parents of children with VUR should be informed that siblings and offspring have a high prevalence of VUR.
- If no screening is performed, prompt treatment of any acute UTIs and subsequent evaluation for VUR should be performed.
- Otherwise, siblings should be screened by US of the kidneys. A VCUG is recommended if there is evidence of renal scarring on US, ureteric dilatation or a history of UTI.
- In older children who are toilet-trained, there is no added value in screening for VUR.

14.2.3 Children with febrile UTI

A VCUG is recommended at 0-2 years of age after the first proven UTI in males and after recurrent UTIs in girls, and in both sexes after the first febrile UTI, respectively. If reflux is diagnosed, further evaluation consists of a DMSA scan. An alternative 'upside-down' approach is also an option, as proven by several studies in the literature. This approach carries out a DMSA scan first, which is then followed by a VCUG if the DMSA scan reveals kidney involvement. A normal DMSA scan with no subsequent VCUG will fail to spot VUR in 5-27% of cases, with the cases of missed VUR being presumably less significant. On the other hand, a normal DMSA with no VCUG will avoid unnecessary VCUGs in more than 50% of those screened (47-50).

14.2.4 Children with LUTS and VUR

Detection of LUTD is essential in treating children with VUR. There are several hypotheses. For example, it is suggested that reflux with LUTD will resolve faster after LUTD correction and that patients with LUTD are at higher risk for developing UTIs and renal scarring (51). Alternatively, it is possible that LUTD is secondary to VUR and that treatment of VUR will therefore result in correction of LUTD. Or it may be that there is a higher co-prevalence, but the treatment of one condition does not correct the other. In recent literature, there is no data to support any of the above hypotheses. Most studies are descriptive, uncontrolled and retrospective and the evidence is low or non-existent.

The recent Swedish reflux study, however, has indicated that patients who have both VUR and LUTD may have a worse final outcome after treatment, including an elevated risk for kidney damage (10). The results from the Swedish study indicate that the co-existence of both conditions should be explored in any patient who has either VUR or LUTD. If there are symptoms suggestive of LUTD (urgency, wetting, constipation or holding manoeuvres), an extensive history and examination, including voiding charts, uroflowmetry and residual urine determination, will reliably diagnose an underlying LUTD.

The other way around is far more complex. In LUTD, VUR is often low grade and US findings are normal. A VCUG is the golden standard for diagnosing a VUR. However, there is no indication for performing a VCUG in all children with LUTD. Instead, it would be more rational to ask any patient with LUTD if he or she has a history of febrile UTI, as there is a greater possibility of finding VUR. However, because of the co-existence of LUTD and VUR, it would be better to do a test covering both problems, such as a video-urodynamic study (VUDS). Any patient with LUTD and a history of febrile UTI should be investigated with VUDS. Furthermore, any child failing standard therapy for LUTD should undergo urodynamic investigation. At this stage, combining a urodynamic study with a VCUG seems good clinical practice.

14.3 Treatment

There are mainly two treatment approaches: conservative or interventional.

14.3.1 Conservative therapy

The objective of conservative therapy is prevention of febrile UTI. It is based on the understanding that:

- VUR resolves spontaneously, mostly in young patients with low-grade reflux; 81% and 48% in VUR grades I-II and III-V, respectively;
- VUR does not damage the kidney when free of infection.

The conservative approach includes watchful waiting, intermittent or continuous antibiotic prophylaxis and bladder rehabilitation in those with LUTD (51-55).

Circumcision during early infancy may be considered as part of conservative approach, as it significantly reduces the risk of infection (56). The most used antibacterial agents for prophylactic treatment are nitrofurantoin (in children > 3 months: 1-2 mg/kg/day, orally) and trimethoprim (in children > 3 months: 2mg/kg/day, orally). In the first 3 months of life, when these agents are poorly absorbed from the gut, amoxicillin (5 mg/kg/day, orally) may be used instead.

14.3.1.1 Follow-up

A regular follow-up with radiographic studies (e.g. VCUG, nuclear cystography, DMSA scan) is part of the conservative management to monitor spontaneous resolution and kidney status. Conservative management should be dismissed in all cases of febrile breakthrough infections, despite antibiotic prophylaxis and intervention should be considered.

14.3.1.2 Continuous antibiotic prophylaxis (CAP)

The use of continuous antibiotic prophylaxis (CAP) and a follow-up scheme during prophylaxis in reflux patients is another area of major controversy. Although it is difficult to make definitive recommendations based on recent literature, it is clear that antibiotic prophylaxis may not be needed in every reflux patient (53,57-59). What is really difficult and risky is to select the group of patients who do not need CAP. A safe approach would be to employ CAP in most instances. Decision-making may be influenced by the presence of risk factors for UTI, such as young age, high-grade VUR, status of toilet-training/LUTS, female gender and circumcision status. However, recent literature does not provide any reliable information about the duration of CAP in reflux patients.

A practical approach would be to use CAP until after children have been toilet-trained and to make sure there is no LUTD. Active surveillance of UTI would be needed after CAP is discontinued. The follow-up scheme and the decision for an anti-reflux procedure or discontinuation of CAP may also depend on personal references and the attitude of the patient and parents. It is strongly advised that the advantages and disadvantages should be discussed in detail with the family.

14.3.2 Interventional treatment

Interventional treatment can be carried out by endoscopic injection of bulking agents or ureteral reimplantation.

14.3.2.1 Subureteric injection of bulking materials

Since this procedure is minimally invasive and performed on an outpatient basis, it has become increasingly popular. Using cystoscopy, bulking materials are injected beneath the intramural part of the ureter in a submucosal location. The injected bulking agent elevates the ureteral orifice and the distal ureter, so that coaptation is increased. This results in narrowing of the lumen, preventing reflux of urine into the ureter, while still allowing its antegrade flow. With the availability of biodegradable substances, endoscopic subureteric injection of bulking agents has become an alternative to long-term antibiotic prophylaxis and surgical intervention in the treatment of VUR in children.

Several bulking agents have been used over the last two decades. These include polytetrafluoroethylene (PTFE or Teflon), collagen, autologous fat, polydimethylsiloxane, silicone, chondrocytes and, more recently, a solution of dextranomer/hyaluronic acid (Deflux).

Although the best results were obtained with PTFE (60), due to concerns about particle migration, PTFE has not been approved for use in children (61). Although they are all biocompatible, other compounds such as collagen and chondrocytes have failed to provide a good outcome. Recently, dextranomer/hyaluronic acid (Deflux) was FDA-approved for the treatment of VUR in children. Initial clinical trials demonstrated that this method was effective in treating reflux (62).

14.3.2.2 Results of Endoscopic anti-reflux procedures

In a meta-analysis (63) including 5527 patients and 8101 renal units, the reflux resolution rate (by ureter) following one treatment for grades I and II reflux was 78.5%, grade III 72%, grade IV 63% and grade V 51%. If the first injection was unsuccessful, the second treatment had a success rate of 68%, and the third treatment 34%. The aggregate success rate with one or more injections was 85%. The success rate was significantly lower for duplicated (50%) versus single systems (73%), and neuropathic (62%) versus normal bladders (74%).

A sound clinical validation of the effectiveness of antireflux endoscopy is currently hampered by the lack of methodologically appropriate studies. In the most recent, prospective, randomised trial comparing three

treatment arms (I, endoscopic injection; II, antibiotic prophylaxis; III, surveillance without antibiotic prophylaxis) in 203 children aged 1-2 years with grade III-IV reflux, endoscopic treatment gave the highest resolution rate of 71% compared to 39% and 47% for treatment arms II and III, respectively, at 2 years' follow-up. The recurrence rate after endoscopic treatment in 2 years was 20%. The occurrence of febrile UTIs and also scar formation was the highest in the surveillance group, at 57% and 11%, respectively. New scar formation rate was higher with an endoscopic injection (7%) compared with the antibiotic prophylaxis group (0%) (64).

14.3.2.3 Open surgical techniques

Various intra- and extra-vesical techniques have been described for the surgical correction of reflux. Although different methods have specific advantages and complications, they all share the basic principle of lengthening the intramural part of the ureter by submucosal embedding of the ureter. All techniques have been shown to be safe with a low rate of complications and excellent success rates (92-98%) (65).

The most popular and reliable open procedure is the cross trigonal reimplantation described by Cohen. The main concern with this procedure is the difficulty of accessing the ureters endoscopically if needed when the child is older. Alternatives are suprahiatal reimplantation (Politano Leadbetter) and infrahiatal reimplantation (Glenn Anderson). If an extravesical procedure (Lich Gregoir) is planned, cystoscopy should be performed pre-operatively to assess the bladder mucosa and the position and configuration of the ureteric orifices. In bilateral reflux, an intravesical antireflux procedure may be considered, as simultaneous bilateral extravesical reflux repair carries an increased risk of temporary post-operative urine retention (66). Overall, all surgical procedures offer very high and similar success rates for correcting the VUR.

14.3.2.4 Laparoscopy

In a few children, VUR has been corrected laparoscopically. Although success rates are similar to open surgery, laparoscopic reflux correction is technically challenging, takes significantly longer, and has no obvious advantages (67). At present, a laparoscopic approach cannot be recommended as a routine procedure (56,68).

14.4 Recommendations for the management of VUR in childhood

Regardless of the grade of reflux or presence of renal scars, all patients diagnosed at infancy should be treated initially with CAP. During early childhood, the kidneys are at higher risk of developing new scars. Immediate, parenteral, antibiotic treatment should be initiated in case of febrile breakthrough infections. A definitive surgical correction is the preferred treatment in patients with breakthrough infections (68).

Surgical correction should be considered in patients with a persistent high-grade reflux (grades IV-V reflux) after a period of antibiotic therapy. There is no consensus about the timing and type of surgical correction. The outcome of open surgical correction is better for higher grades of reflux, while endoscopic injection may be an option for lower grades of reflux.

There is no evidence for correction of persistent low-grade reflux (grades I-III) without symptoms. These patients may be candidates for endoscopic treatment. In all children presenting at later ages (1-5 years), CAP is the preferred option as an initial therapy. For those with high-grade reflux, surgical repair is a reasonable alternative. In patients with lower grades of reflux and without symptoms, close surveillance without antibiotic prophylaxis may be an option.

A meticulous investigation for the presence of LUTS and LUTD should be performed in all children after toilet-training. If LUTD is found, the initial treatment should always be for LUTD.

If parents prefer definitive therapy to conservative management while receiving antibiotic prophylaxis, surgical correction may be considered. Endoscopic treatment is an option for all children with low grades of reflux and those not wishing to receive further antibiotics.

The traditional approach of initial medical treatment after diagnosis and shifting to interventional treatment in case of breakthrough infections and new scar formation needs to be challenged, as the treatment should be tailored to different risk groups.

The choice of management depends on the presence of renal scars, clinical course, grade of reflux, ipsilateral renal function, bilaterality, bladder function, associated anomalies of the urinary tract, age, compliance and parental preference. Presentation with a febrile UTI, high-grade reflux, bilaterality and cortical abnormalities is considered as a risk factor for possible renal damage. The presence of LUTD is an additional risk factor for new scars.

In high-risk patients who already have renal impairment, a more aggressive approach with a multidisciplinary team is needed. Table 2 summarises the management of different risk groups.

Table 2: Management and follow-up according to different risk groups

Risk Groups	Presentation	Initial treatment		Follow-up
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grades IV-V), abnormal kidneys and LUTD	Initial treatment is always for LUTD with CAP; intervention may be considered in cases of BT infections or persistent reflux	Greater possibility of earlier intervention	More aggressive follow-up for UTI and LUTD; full re-evaluation after 6 months
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grade IV-V), abnormal kidneys and no LUTD	Intervention should be considered	Open surgery has better results than endoscopic surgery	Post-operative VCUG on indication only; follow-up of kidney status until after puberty
Moderate	Symptomatic male or female patients before toilet-training, with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT infections or persistent reflux	Spontaneous resolution is higher in males	Follow-up for UTI/hydronephrosis; full re-evaluation after 12-24 months
Moderate	Asymptomatic patients (PNH or sibling) with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT, infections or persistent reflux		Follow-up for UTI/hydronephrosis; full re-evaluation after 12-24 months
Moderate	Symptomatic male or female patients after toilet-training, with high-grade reflux and normal kidneys with LUTD	Initial treatment is always for LUTD with CAP. Intervention may be considered in cases of BT, infections or persistent reflux	In case of persistent LUTD, despite urotherapy, intervention should be considered. The choice of intervention is controversial	Follow-up for UTI and LUTD, kidney status; full re-evaluation after successful urotherapy
Moderate	Symptomatic male or female patients after toilet-training with low-grade reflux, abnormal kidneys with or without LUTD	Choice of treatment is controversial. Endoscopic treatment may be an option. LUTD treatment should be given if needed.		Follow-up for UTI, LUTD, and kidney status until after puberty
Moderate	All symptomatic patients with normal kidneys, with low-grade reflux, with LUTD	Initial treatment is always for LUTD with or without CAP		Follow-up for UTI and LUTD
Low	All symptomatic patients with normal kidneys, with low-grade reflux, with no LUTD	No treatment or CAP	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI
Low	All asymptomatic patients with normal kidneys with low-grade reflux	No treatment or CAP in infants	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI

BT = breakthrough; CAP = continuous antibiotic prophylaxis; LUTD = lower urinary tract dysfunction; PNH = prenatal diagnosed Hydronephrosis; UTI = urinary tract infection.

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15. URINARY STONE DISEASE

15.1 Background

Paediatric stone disease is an important clinical problem in paediatric urology practice. Because of its recurrent nature, every effort should be made to discover the underlying metabolic abnormality so that it can be treated appropriately. Obtaining a stone-free state with interventional management and close follow-up are of utmost importance.

Paediatric stone disease has its own unique features, which are different in both presentation and treatment compared to stone disease in adults. In contrast to adults with stone disease who are more likely to be male, boys and girls are affected almost equally. Most paediatric stones are located in the upper urinary tract. However, bladder stones are still common in underdeveloped areas of the world and are usually ammonium acid urate and uric acid stones, strongly implicating dietary factors (1).

The incidence and characteristics of stones show a wide geographical variation in children. Although urinary stone disease is generally considered to be a relatively rare disease, it is quite common in some parts of the world. Paediatric stone disease is endemic in Turkey, Pakistan and in some South Asian, African and South American states. In the UK and other European countries, 75% of calculi in children are composed of organic

matrix and struvite, with many coinciding with Proteus infection and urinary tract anomalies (2).

15.2 Stone formation mechanisms, diagnosis of causative factors and medical treatment for specific stone types

Urinary stone formation is the result of a complex process involving metabolic, anatomical factors and presence of infection.

When supersaturated in urine calcium, oxalate, uric acid and cystine molecules may cause stone formation. A decreased concentration of crystallisation inhibitors (citrate, magnesium, pyrophosphate, macromolecules and glycosaminoglycans) may sometimes be the sole factor playing a role in the formation of urinary stones. Urinary pH changes also affect stone formation.

An impaired flow of urine due to abnormal morphology may facilitate stasis and increase the concentration of stone-forming substances.

15.2.1 Calcium stones

Calcium stones are usually made from calcium oxalate or calcium phosphate. Either supersaturation of calcium (hypercalciuria) and oxalate (hyperoxaluria) or decreased concentration of inhibitors like citrate (hypocitraturia) play a major role in calcium oxalate stone formation.

Hypercalciuria. This is defined by a 24-hour urinary calcium excretion of more than 4 mg/kg/day in a child weighing less than 60 kg. In infants younger than 3 months, 5 mg/kg/day is considered to be the upper limit of normal for calcium excretion (3).

Hypercalciuria can be classified as either idiopathic or secondary. Idiopathic hypercalciuria is diagnosed when clinical, laboratory, and radiographic investigations fail to delineate an underlying cause. Secondary hypercalciuria occurs when a known process produces excessive urinary calcium. In secondary (hypercalcaemic) hypercalciuria, a high serum calcium level may be due to increased bone resorption (hyperparathyroidism, hyperthyroidism, immobilisation, acidosis, metastatic disease) or gastrointestinal hyperabsorption (hypervitaminosis D) (4).

A good screening test for hypercalciuria compares the ratio of urinary calcium to creatinine. The normal calcium-to-creatinine ratio in children is less than 0.2. If the calculated ratio is higher than 0.2, repeat testing is indicated. Neonates and infants have a higher calcium excretion and lower creatinine excretion than older children (3,4). If the follow-up ratios are normal, then no additional testing for hypercalciuria is needed. However, if the ratio remains elevated, a timed 24-hour urine collection should be obtained and the calcium excretion calculated.

The 24-hour calcium excretion test is the criterion standard for the diagnosis of hypercalciuria. If calcium excretion is higher than 4 mg/kg/day (0.1 mmol/kg/day), the diagnosis of hypercalciuria is confirmed and further evaluation is warranted. Further evaluation includes levels of serum bicarbonate, creatinine, alkaline phosphatase, calcium, magnesium, pH, and parathyroid hormone. Freshly voided urine should be measured for pH (3-6).

A 24-hour urine collection should also be collected for measurement of calcium, phosphorus, sodium, magnesium, citrate and oxalate. Meanwhile dietary manipulations should be tried to normalise urine calcium (6).

Initial management is always to increase fluid intake and urinary flow. Dietary modification is a mandatory part of effective therapy. The child should be referred to a dietician to assess accurately the daily intake of calcium, animal protein, and sodium. Dietary sodium restriction is recommended as well as maintenance of calcium intake consistent with the daily needs of the child (7).

A brief trial of a low-calcium diet can be carried out to determine if exogenous calcium intake is contributing to a high urinary calcium. However, great caution should be used when trying to restrict calcium intake for long periods (LE: 3; GR: B).

Hydrochlorothiazide and other thiazide-type diuretics may be used to treat hypercalciuria at a dosage of 1-2 mg/kg/day (2, 8) (LE: 3; GR: C). Citrate therapy is also useful if citrate levels are low or if hypercalciuria persists, despite other therapies (2, 9) (LE: 4; GR: C).

Hyperoxaluria. Oxalic acid is a metabolite excreted by the kidneys. Only 10-15% of oxalate comes from diet. Normal school children excrete less than 50 mg (0.57 mmol)/1.73m²/day (2, 10), while infants excrete four times as much. Hyperoxaluria may result from increased dietary intake, enteric hyperabsorption (as in short bowel syndrome) or an inborn error of metabolism.

In primary hyperoxaluria, one of the two liver enzymes that play a role in the metabolism of oxalate may be deficient. In primary hyperoxaluria there is increased deposition of calcium oxalate in the kidney and in urine. With increased deposition of calcium oxalate in the kidneys, renal failure may ensue in resulting deposition of calcium oxalate in other tissues. The diagnosis is made upon laboratory findings of severe

hyperoxaluria and clinical symptoms. The definitive diagnosis requires liver biopsy to assay the enzyme activity.

Other forms of hyperoxaluria, as mentioned earlier, may be due to hyperabsorption of oxalate in inflammatory bowel syndrome, pancreatitis and short bowel syndrome. Yet, the majority of children who have high levels of oxalate excretion in urine may not have any documented metabolic problem or any dietary cause. This is known as idiopathic 'mild' hyperoxaluria, with urine oxalate levels elevated only mildly in these cases. The treatment of hyperoxaluria consists of the promotion of high urine flow, restriction of dietary oxalate and regular calcium intake. Pyridoxine may be useful in reducing urine levels, especially in primary hyperoxaluria (2,10) (LE: 4; GR: C).

Hypocitraturia. Citrate is a urinary stone inhibitor. Citrate acts by binding to calcium and by directly inhibiting the growth and aggregation of calcium oxalate as well as calcium phosphate crystals. Thus, low urine citrate may be a significant cause of calcium stone disease. In adults, hypocitraturia is the excretion of citrate in urine of less than 320 mg/day (1.5 mmol/day) for adults; this value must be adjusted for children depending on body size (11,12).

Hypocitraturia usually occurs in the absence of any concurrent symptoms or any known metabolic derangements. It may also occur in association with any metabolic acidosis, distal tubular acidosis or diarrhoeal syndromes.

Environmental factors that lower urinary citrate include a high protein intake and excessive salt intake. Many reports emphasise the significance of hypocitraturia in paediatric calcium stone disease. The presence of hypocitraturia ranges from 30% to 60% in children with calcium stone disease.

Due to the increased stone risk in hypocitraturia, the restoration of normal citrate levels is advocated to reduce stone formation. Although some studies have shown that citrate replacement therapy reduces the risk of stone formation in an adult population, there are few relevant studies in children. Hypocitraturia is treated by potassium citrate at a starting dose of 1 mEq/kg, given in two divided doses (12) (LE: 3; GR: B).

15.2.2 **Uric acid stones**

Uric acid stones are responsible for urinary calculi in 4-8% of children. Uric acid is the end product of purine metabolism. Hyperuricosuria is the main cause of uric acid stone formation in children. A daily output of uric acid of more than 10 mg/kg/day is considered to be hyperuricosuria (2).

The formation of uric acid stones is dependent, mainly on the presence of acidic urinary composition. Uric acid dissociation and solubility is strongly reduced at pH of less than 5.8. As the pH becomes more alkaline, uric acid crystals become more soluble and the risk of uric acid stone formation is reduced.

In the familial or idiopathic form of hyperuricosuria, children usually have normal serum uric acid levels. In other children, it can be caused by uric acid overproduction secondary to inborn errors of metabolism, myeloproliferative disorders or other causes of cell breakdown. Hyperuricosuria is also caused by high purine and protein intake. Although hyperuricosuria is a risk factor for calcium oxalate stone formation in adults, this does not appear to be a significant risk factor in children.

Uric acid stones are non-opaque stones. Plain X-rays are insufficient to show uric acid stones, and renal sonography and spiral CT are used for diagnosis.

Alkalinisation of urine is the mainstay of therapy and prevention for uric acid stones. Citrate preparations are useful as alkalinising agents. Maintaining a urine pH of 6 to 6.5 is sufficient to prevent uric acid stones (2).

15.2.3 **Cystine stones**

Cystinuria is the cause of cystine stone formation and accounts for 2-6% of all urinary stones in children. Cystinuria is an incompletely recessive autosomal disorder characterised by failure of renal tubules to reabsorb four basic amino acids, cystine, ornithine, lysine and arginine.

Of these four amino acids, only cystine has poor solubility in urine, so that only cystine stones may form in the case of excessive excretion in urine. Cystine solubility is pH-dependent, with cystine precipitation beginning at pH levels < 7.0. Other metabolic conditions, such as hypercalciuria, hypocitraturia and hyperuricosuria, may accompany cystinuria, so leading to the formation of mixed-composition stones.

Cystine stones are faintly radiolucent and may be difficult to show on regular radiograph studies. They are also hard in texture and more difficult to disintegrate by extracorporeal shock-wave lithotripsy (ESWL).

The medical treatment for cystine stones aims to reduce cystine saturation in urine and increase its solubility. The initial treatment consists of maintaining a high urine flow and the use of alkalinising agents, such as potassium citrate to maintain urine pH at above 7.0. If this treatment fails, the use of α -mercaptopyronil glycine or D-penicillamine may reduce cystine levels in urine and prevent stone formation. Use of these drugs can be associated with severe side effects, such as bone marrow depression and nephrotic syndrome (13) (LE: 4; GR: C).

15.2.4 **Infection stones (struvite stones)**

Infection-related stones constitute nearly 5% of urinary stones in children. Bacteria capable of producing urease enzyme (*Proteus*, *Klebsiella*, *Pseudomonas*) are responsible for the formation of such stones.

Urease converts urea into ammonia and bicarbonate, so alkalising the urine and further converting bicarbonate into carbonate. In the alkaline environment, triple phosphates form, eventually resulting in a supersaturated environment of magnesium ammonium phosphate and carbonate apatite, which in turn leads to stone formation.

In addition to bacterial elimination, stone elimination is essential for treatment, as stones will harbour infection and antibiotic treatment will not be effective. Consideration should be given to investigating any congenital problem that causes stasis and infection. Genitourinary tract anomalies predispose to formation of such stones.

15.3 **Clinical presentation**

Presentation tends to be age-dependent, with symptoms such as flank pain and haematuria being more common in older children. Non-specific symptoms (e.g. irritability, vomiting) are common in very young children. Haematuria, usually gross, occurring with or without pain, is less common in children. However, microscopic haematuria may be the sole indicator and is more common in children. In some cases, urinary infection may be the only finding leading to radiological imaging in which a stone is identified (14,15).

15.4 **Diagnosis**

15.4.1 **Imaging**

Generally, ultrasonography should be used as a first study. Renal ultrasonography is very effective for identifying stones in the kidney. Many radiolucent stones can be identified with a simple abdominal flat-plate examination.

If no stone is found but symptoms persist, spiral CT scanning is indicated. The most sensitive test for identifying stones in the urinary system is non-contrast helical CT scanning. It is safe and rapid, with 97% sensitivity and 96% specificity (16-18) (LE: 2; GR: B).

Intravenous pyelography is rarely used in children, but may be needed to delineate the caliceal anatomy prior to percutaneous or open surgery.

15.4.2 **Metabolic evaluation**

Due to the high incidence of predisposing factors for urolithiasis in children and high stone recurrence rates, every child with urinary stone should be given a complete metabolic evaluation (1,19,20).

Metabolic evaluation includes:

- Family and patient history of metabolic problems.
- Analysis of stone composition (following stone analysis, metabolic evaluation can be modified according to the specific stone type).
- Electrolytes, BUN, creatinine, calcium, phosphorus, alkaline phosphatase, uric acid, total protein, carbonate, albumin, and parathyroid hormone (if there is hypercalcaemia).
- Spot urinalysis and culture, including ratio of calcium to creatinine.
- Urine tests, including a 24-hour urine collection for calcium, phosphorus, magnesium, oxalate, uric acid citrate, cystine, protein, and creatinine clearance.

Figure 3 provides an algorithm of how to perform metabolic investigations in urinary stone disease in children and to plan medical treatment accordingly.

15.5 **Management**

With the advance of technology stone management has changed from open surgical approach to endoscopic techniques that are less invasive. Deciding the form of treatment depends on the number, size, location, composition and anatomy of the urinary tract (19,21,22).

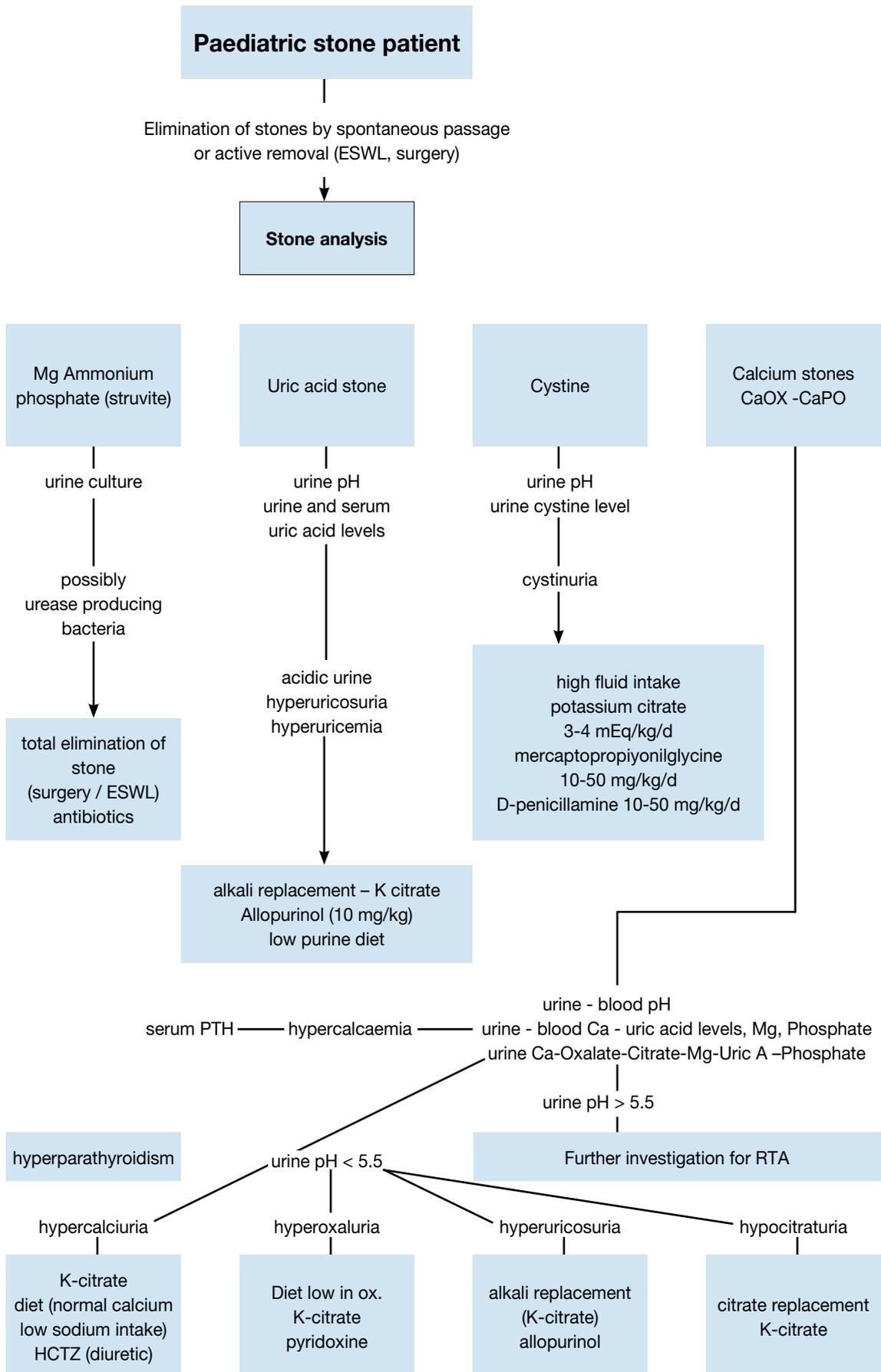
Currently, most paediatric stones can easily be managed by ESWL. Endoscopic treatment can be applied easily for ureteric and bladder stones. Percutaneous removal of stones is also possible for kidney stones in children. Only a small portion of children will need an open surgical approach.

15.5.1 **Extracorporeal shock-wave lithotripsy (ESWL)**

Many reports confirm that shock-wave lithotripsy (SWL) can be performed in children with no suspicion of long-term morbidity of the kidney (23-28).

The mean number of shock waves for each treatment is about 1800 and 2000 (up to 4000 if needed) and the mean power set varies between 14kV and 21 kV. The use of ultrasonography and digital fluoroscopy has significantly decreased the radiation exposure and it has been shown that children are exposed to significantly lower doses of radiation compared to adults (21,29,30). Concerns about anaesthesia do not seem

Figure 3: Algorithm of how to perform metabolic investigations in urinary stone disease in children



ESWL = extracorporeal shockwave lithotripsy; HCTZ = hydrochlorothiazide; PTH = parathyroid hormone; RTA = renal tubular acidosis

to be a problem any more because of advances in technique and medication, even in the infant period. The type of anaesthesia should be general or dissociative for children under 10 years of age, whereas conventional intravenous sedation or patient-controlled analgesia is an option for older children who are able to co-operate (31) (LE: 2b).

Stone-free rates are significantly affected by various factors. Regardless of the location, as the stone size increases, the stone-free rates decrease and re-treatment rate increases. The stone-free rates for < 1 cm, 1-2 cm, > 2 cm and overall were reported as nearly 90%, 80%, 60% and 80%, respectively. As the stone size increases, the need for additional sessions increases (21, 29, 30, 32-36).

Localisation of the calculi has been described as a significant factor affecting the success rates in different studies. Stones in renal pelvis and upper ureter seem to respond better to SWL. In these mentioned sites, the stone clearance rates are nearly 90%. However, SWL was found to be less effective for caliceal stones particularly the lower caliceal stones. Several studies reported stone-free rates for isolated lower caliceal stones varying between 50% and 62% (37-40).

ESWL treatment can also be used to treat ureteral calculi. However, this is a more specific issue and with controversies. The success rates with ESWL are less for distal ureteric stones. There may also be technical problems with localisation and focusing of ureteric stones in children (37, 39, 40-42).

The type of machine used has a strong effect on success rates and complications. First-generation machines can deliver more energy to a larger focal zone, resulting in higher fragmentation rates in a single therapy. However, general anaesthesia is usually required due to the intolerable discomfort associated with a first-generation machine. Later-generation machines have a smaller focal zone and deliver less energy, and have a lower risk of pulmonary trauma. However, additional treatments may be needed with later-generation machines. The success rate is higher in younger children (35).

Although stenting does not affect stone clearance, overall complication rates are higher and hospital stay is longer in the unstented patient (34, 35). Stenting is essential in solitary kidneys undergoing ESWL treatment. Children with a large stone burden have a high risk of developing Steinstrasse and urinary obstruction and should be followed more closely for the risk of prolonged urinary tract obstruction after ESWL. Post-ESWL stent or nephrostomy tube placement may be needed in prolonged obstruction (20, 36).

ESWL in children may have complications, but these are often self-limiting and transient. The most frequently observed complications are:

- Renal colic
- Transient hydronephrosis
- Dermal ecchymosis
- Urinary tract infection
- Formation of Steinstrasse
- Sepsis
- Rarely, haemoptysis.

In children with sterile pre-operative urine cultures, antibiotic prophylaxis to decrease the infectious complications is not recommended (43). However, every effort should be made to sterilise the urine before performing ESWL, ureteroscopy (URS), or percutaneous nephrolithotomy.

15.5.2 **Percutaneous nephrolithotomy**

ESWL is the first choice for treating most renal paediatric stones. However, percutaneous renal surgery can be used for larger and complex stones. Pre-operative evaluation, indication and surgical technique are similar in children compared to adults. PCNL is used as monotherapy in most cases, but is also used as an adjunctive procedure to other therapies.

The use of adult-sized instruments, in association with an increased number of tracts and sheath size, seems to increase the blood loss. However, small-calibre instruments have now been developed and there are some advantages for PCNL in children (particularly smaller children), such as smaller skin incision, single-step dilation and sheath placement, good working access for paediatric instruments, variable length, and lower cost (43, 44). Now that appropriate-size instruments are available, age is no longer a limiting factor for PCNL.

As monotherapy, PCNL is considerably effective and safe. The reported stone-free rates in the recent literature are between 86.9% and 98.5% after a single session. These rates increase with adjunctive measures, such as second-look PCNL, ESWL and URS. Even in complete staghorn cases, a clearance rate of 89% has been achieved following a single session (45-48,50,51).

The most frequently reported complications of PCNL in children are bleeding, post-operative fever or infection, and persistent urinary leakage. Bleeding requiring transfusion is reported in 0.4% to 23.9% and is closely associated with stone burden, operative time, sheath size and number of tracts. Post-operative fever and infection has been reported up to 29.3% and 5.5%, respectively; the origin of fever is not thought to be the infection (49-56).

The mean post-operative hospital stay is similar to adults. It is reported as 3 to 4 days in all the

previously mentioned studies and is much shorter than open surgery. The less invasive nature of this technique has made it a promising alternative to open surgery for treating renal stones in children (LE: 2; GR: B).

15.5.3 Ureterorenoscopy

The increasing availability of smaller size endourological equipment has made it possible to manage paediatric ureteral stones using endoscopic techniques.

The technique used in children is similar to the one used in adults. It is strongly recommended that guide wires are used and the procedure is performed using direct vision. Routine balloon dilation of ureterovesical junction and ureteral stenting are controversial. In general, ureteric dilatation is being done less and less and only in selected cases. The general tendency is to use hydrodilatation more as it is shown to be as effective (57-60,43,61-63) (LE: 3; GR: B).

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, have all been shown to be safe and effective. Because of the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases (50, 58, 60, 64-70).

All studies reporting the use of endoscopy for ureteric stones in children have clearly demonstrated that there is no significant risk of ureteric strictures or reflux with this mode of therapy (LE: 1; GR: A).

15.5.4 Open stone surgery

Most stones in children can be managed by ESWL and endoscopic techniques. Yet in some situations, open surgery is inevitable. Good candidates for open stone surgery include very young children with large stones and/or a congenitally obstructed system which also requires surgical correction. Severe orthopaedic deformities may limit positioning for endoscopic procedures. Open surgery would also be a necessity for such children.

Bladder stones in children can usually be managed by endoscopic techniques. Open surgery may also be used for very large bladder stones or for bladder stones caused by an anatomical problem. Recommendations for interventional management are given in Table 3.

Table 3: Recommendations for interventional management in paediatric stones

Stone size and localisation*	Primary treatment option	LE	Secondary treatment options	
Staghorn stones	PCNL	2b	Open/SWL	Multiple sessions and accesses with PCNL may be needed Combination with SWL may be useful
Pelvis < 10 mm	SWL	1a	RIRS/PCNL	
Pelvis 10-20 mm	SWL	2b	PCNL/Open	Multiple sessions with SWL may be needed PCNL has similar recommendation grade
Pelvis > 20 mm	PCNL	2b	SWL/Open	Multiple sessions with SWL may be needed
Lower pole calix < 10 mm	SWL	2c	RIRS/PCNL	Anatomical variations are important for complete clearance after SWL
Lower pole calix > 10 mm	PCNL	2b	SWL	Anatomical variations are important for complete clearance after SWL
Upper ureteric stones	SWL	2b	PCNL/URS/ Open	
Lower ureteric stones	URS	1a	SWL/Open	Additional intervention need is high with SWL
Bladder stones	Endoscopic	2b	Open	Open is easier and with less operative time with large stones

* Cystine and uric acid stones excluded.

LE = level of evidence; PCNL = percutaneous nephrolithostomy; SWL = shock-wave lithotripsy; RIRS = retrograde intrarenal surgery; URS = ureteroscopy.

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16. OBSTRUCTIVE PATHOLOGY OF RENAL DUPLICATION: URETEROCELE AND ECTOPIC URETER

16.1 Background

Ureterocele and ectopic ureter are the two main anomalies associated with a complete renal duplication. At present, antenatal ultrasonography detects both conditions in the majority of cases and diagnosis is confirmed after birth by further examination. Later on in life, these anomalies are revealed by clinical symptoms: UTI, pain, disturbances of micturition and urinary incontinence.

16.1.1 Ureterocele

Ureterocele is a cystic dilatation developed on the intravesical part of the ureter corresponding to the upper pole of a renal duplication. It is more frequent in females than in males, the overall prevalence being 1 in 4,000 births.

16.1.2 Ectopic ureter

Ectopic ureter is less frequent than ureterocele (1 in 40,000 births), but is again more common in females (male to female ratio, 1:5). Eighty per cent of ectopic ureters are associated with a complete renal duplication.

In females, the ureteral orifice may be located:

- in the urethra, from bladder neck to meatus (35%)
- in the vaginal vestibule (30%)
- in the vagina (25%)
- in the uterus and Fallopian tube (rarely).

In males, the ureteral orifice may be located:

- in the posterior urethra above the verumontanum and never below the external sphincter (60%)
- in the seminal tract (vas deferens, ejaculatory ducts, seminal vesicles) (40%).

16.2 Classification

Ureterocele is usually obstructive for the upper pole moiety, but the degree of obstruction and functional impairment is variable according to the type of ureterocele and upper pole dysplasia. In the orthotopic form, there is often no, or only mild, obstruction and frequently the function of the moiety is normal or slightly impaired; the corresponding ureter may be dilated. In the ectopic form, the upper pole is altered, frequently dysplastic and hypofunctional or non-functional. The corresponding ureter is a megaureter. In the caecoureterocele (see definition below), the upper pole of the renal duplication is always dysplastic and non-functional.

16.2.1 Ectopic ureterocele

Ectopic ureterocele is the most common form of ureterocele (> 80%) and occurs bilaterally in about 40% of cases. It is voluminous, dissociating the trigone and slipping into the urethra, and can rarely prolapse through the urethral meatus. The ureterocele orifice is tight, rarely large, and located near the bladder neck, either in the bladder itself or in the urethra below the bladder neck. The ureter corresponding to the lower pole moiety is raised by the ureterocele and is frequently refluxing or compressed by the ureterocele, leading to an obstructive megaureter. A contralateral renal duplication is associated in 50% of cases. Occasionally, very large ureteroceles are responsible for reflux or obstruction of the contralateral upper tract.

16.2.2 Orthotopic ureterocele

Orthotopic ureterocele accounts for 15% of cases. It is exclusively observed in females, and is small and located strictly intravesically. Orthotopic ureteroceles are mostly combined with a single kidney system.

16.2.3 Caecoureterocele

Caecoureterocele is very rare, occurring in less than 5% of cases. It is associated with an ectopic ureter and located in the urethra below the bladder neck.

16.3 Diagnosis

16.3.1 Ureterocele

Prenatal ultrasound reveals easily voluminous obstructive ureteroceles. In cases of a very small upper pole or a slightly obstructive ureterocele, prenatal diagnosis will be difficult. If prenatal diagnosis has been impossible, the following clinical symptoms - beside incidental findings - can reveal the congenital anomaly at birth or later:

- at birth, a prolapsed and sometimes strangulated ureterocele may be observed in front of the urethral orifice. In a newborn boy, it might cause acute urinary retention, simulating urethral valves
- the early symptom of pyelonephritis in either sex may lead to the diagnosis
- later symptoms can include dysuria, recurrent cystitis and urgency.

In cases of prenatal diagnosis at birth, ultrasonography confirms the ureteral dilatation ending at the upper pole of a renal duplication. It also demonstrates the presence of an ureterocele in the bladder, with a dilated ureter behind the bladder.

At this point, it is important to assess the function of the upper pole using nuclear renography in the region of interest. Magnetic resonance urography may visualise the morphological status of the upper pole and lower moieties and of the contralateral kidney. A VCUG is mandatory in identifying an ipsilateral or contralateral reflux and to assess the degree of intraurethral prolapse of the ureterocele.

Urethrocystoscopy may reveal the pathology in cases where it is difficult to make the differential diagnosis between ureterocele and ectopic megaureter.

16.3.2 Ectopic ureter

Most of the ectopic megaureters are diagnosed primarily by ultrasound. In some cases, clinical symptoms can lead to diagnosis:

- in neonates: dribbling of urine, pyuria and acute pyelonephritis

- an ectopic orifice may be found in the meatal region. Significant vaginal discharge may be the equivalent of incontinence in little girls
- in pre-adolescent males: epididymitis is the usual clinical presentation and a palpable seminal vesicle may be found on digital rectal examination.

Ultrasonography, nuclear studies, VCUG, MR urography and cystoscopy are the diagnostic tools to assess function, to detect reflux and to rule out ipsilateral compression of the lower pole and urethral obstruction. In the clarification of incontinence in girls, a methylene blue filling of the bladder can be helpful: in the case of loss of uncoloured urine, an ectopic ureter must be present.

16.4 Treatment

16.4.1 Ureterocele

The management is controversial with the choice between endoscopic decompression, partial nephro-ureterectomy or complete primary reconstruction. The choice of a therapeutic modality depends on the following criteria: clinical status of the patient (e.g. urosepsis), age of the patient, renal function of the upper pole, presence or absence of reflux, obstruction of the ipsilateral ureter, pathology of the contralateral ureter, and parents' and surgeon's preferences.

16.4.1.1 Early diagnosis

- in a clinically asymptomatic child with an ureterocele and non- or hypo-functional upper pole, without significant obstruction of the lower pole and without bladder outlet obstruction, prophylactic antibiotic treatment is given until follow-up procedures are instigated
- in the presence of severe obstruction and infection, an immediate endoscopic incision or puncture is recommended.

16.4.1.2 Re-evaluation

If decompression is effective and there is no reflux (approximately 25% of cases), the patient is followed-up conservatively. Secondary surgery is necessary if decompression is not effective, significant reflux is present or there is obstruction of the ipsi- or contra-lateral ureters and/or bladder neck obstruction. Surgery may vary from partial nephrectomy to complete unilateral reconstruction.

16.4.2 Ectopic ureter

In the majority of cases, the upper pole is dysplastic and heminephro-ureterectomy should be considered. Ureteral reconstruction is a therapeutic option in cases in which the upper pole has function worth preserving.

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17. DISORDERS OF SEX DEVELOPMENT

17.1 Background

The formerly called 'intersex disorders' were recently the subject of a consensus document in which it was decided that the term 'intersex' should be changed to 'disorders of sex development' (DSD) (1, 2).

The new classification has arisen because of advances in knowledge of the molecular genetic causes of abnormal sexual development, controversies inherent to clinical management and ethical issues. Controversial and pejorative terminology, e.g. 'pseudohermaphroditism' and 'hermaphroditism', have been renamed according to the new pathophysiological insights. Furthermore, some conditions presenting with severe male genital malformation, such as penile agenesis, cloacal exstrophy, which could not be categorised, have also been included. The term 'disorders of sex development' is proposed to indicate congenital conditions with atypical development of chromosomal, gonadal or anatomical sex.

We refer to the consensus document as a general guideline, while this chapter will focus on what is relevant for the practising paediatric urologist. As the urologist is likely to be involved in both surgical and non-surgical neonatal work, this chapter will discuss the neonatal emergency and the diagnostic and therapeutic role of the paediatric urologist.

Overall, there is a low evidence base for the published literature on DSD. There are no randomised controlled trials and most studies are based on retrospective clinical descriptive studies (grade 4 level of evidence) or are expert opinion. An exception is the risk of gonadal cancer, for which the level of evidence is higher.

Disorders of sex development require a multidisciplinary approach to diagnosis and treatment, which should include geneticists, neonatologists, paediatric and adult endocrinologists, gynaecologists, psychologists, ethicists and social workers. Each team member should be specialised in DSD and a team should have enough new patients to ensure experience.

17.2 The neonatal emergency

The first step is to recognise the possibility of DSD (Table 4) and to refer the newborn baby immediately to a tertiary paediatric centre, fully equipped with neonatal, genetics, endocrinology and paediatric urology units. At the paediatric centre, the situation should be explained to the parents fully and kindly. Registering and naming the newborn should be delayed as long as necessary.

17.2.1 Family history and clinical examination

A careful family history must be taken followed by a thorough clinical examination (Table 5).

Table 4: Findings in a newborn suggesting the possibility of DSD (adapted from the American Academy of Pediatrics)

Apparent male

- Severe hypospadias associated with bifid scrotum
- Undescended testis/testes with hypospadias
- Bilateral non-palpable testes in a full-term apparently male infant

Apparent female

- Clitoral hypertrophy of any degree, non-palpable gonads
- Vulva with single opening

Indeterminate

- Ambiguous genitalia

Table 5: Diagnostic work-up of neonates with ambiguous genitalia

<p>History (family, maternal, neonatal)</p> <ul style="list-style-type: none">• Parental consanguinity• Previous DSD or genital anomalies• Previous neonatal deaths• Primary amenorrhoea or infertility in other family members• Maternal exposure to androgens• Failure to thrive, vomiting, diarrhoea of the neonate <p>Physical examination</p> <ul style="list-style-type: none">• Pigmentation of genital and areolar area• Hypospadias or urogenital sinus• Size of phallus• Palpable and/or symmetrical gonads• Blood pressure <p>Investigations</p> <ul style="list-style-type: none">• Blood analysis: 17-hydroxyprogesterone, electrolytes, LH, FSH, TST, cortisol, ACTH• Urine: adrenal steroids• Karyotype• Ultrasound• Genitogram• hCG stimulation test• Androgen-binding studies• Endoscopy
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LH = luteinising hormone; FSH = follicle stimulating hormone; TST = testosterone; ACTH = adrenocorticotrophic hormone; hCG = human chorionic gonadotrophin.

17.2.2 Choice of laboratory investigations

The following laboratory investigations are mandatory:

- Karyotype
- Plasma 17-hydroxyprogesterone assay
- Plasma electrolytes
- Ultrasonography to evaluate the presence of Müllerian duct structures.

These investigations will provide evidence of congenital adrenal hyperplasia (CAH), which is the most frequently occurring DSD. If this evidence is found, no further investigation is needed. If not, then the laboratory work-up should proceed further.

The hCG stimulation test is particularly helpful in differentiating the main syndromes of 46XYDSD by evaluating Leydig cell potential. When testosterone metabolism is evaluated, the presence or absence of metabolites will help to define the problem. An extended stimulation can help to define phallic growth potential and to induce testicular descent in some cases of associated cryptorchidism.

17.3 Gender assignment

This is a very complicated task. It should take place after a definitive diagnosis has been made. The idea that an individual is sex-neutral at birth and that rearing determines gender development is no longer the standard approach. Instead, gender assignment decisions should be based upon:

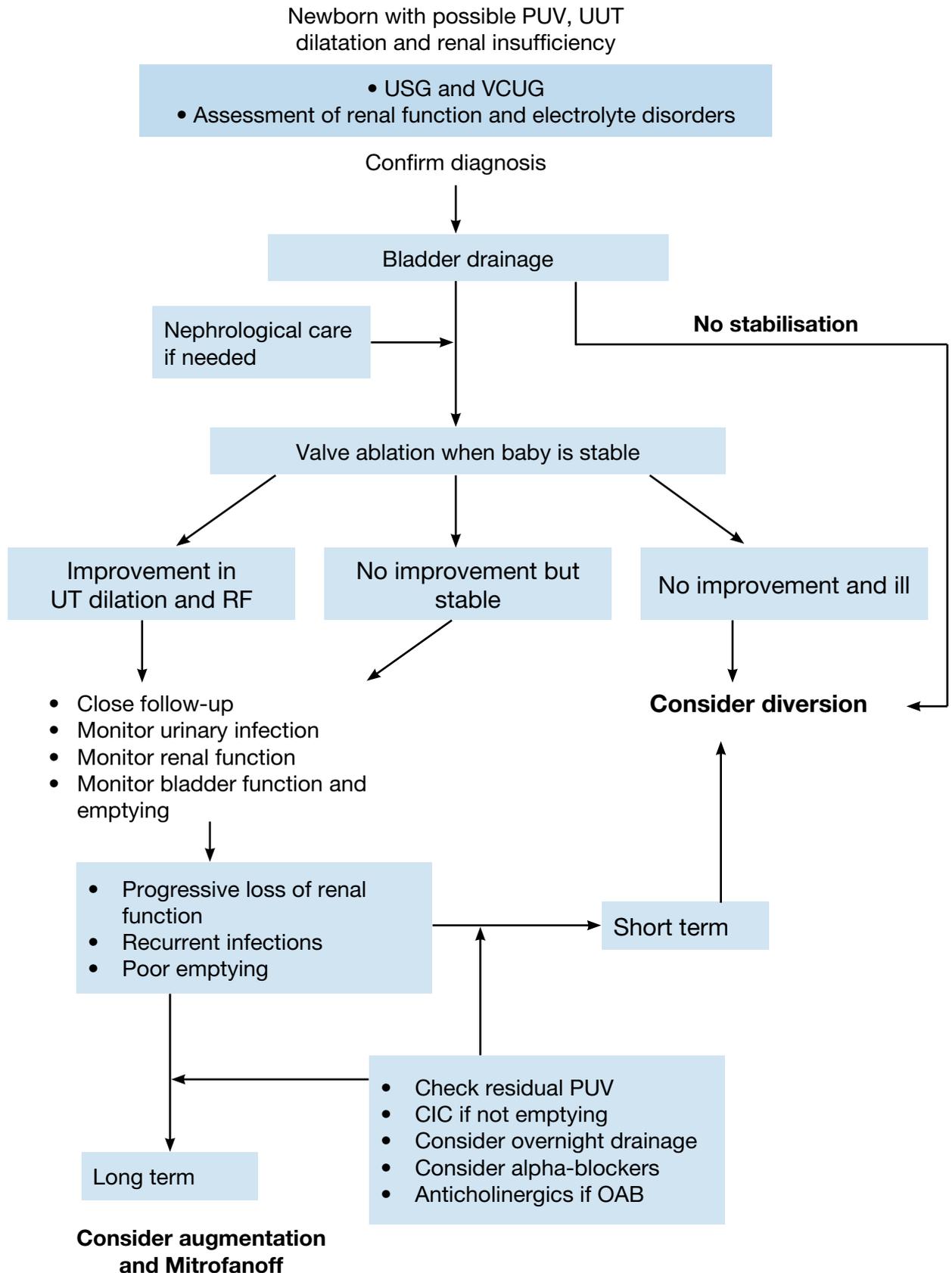
- Age at presentation
- Fertility potential
- Size of the penis
- Presence of a functional vagina
- Endocrine function
- Malignancy potential
- Antenatal testosterone exposure
- General appearance
- Psychosocial well-being and a stable gender identity.

Each patient presenting with DSD should be assigned a gender as quickly as a thorough diagnostic evaluation permits.

17.4 Role of the paediatric urologist

The role of the paediatric urologist can be divided into a diagnostic role and a therapeutic role (Table 6). Each of these roles will be discussed briefly.

Figure 4: An algorithm providing information on assessment, treatment and follow-up of newborns with possible PUV



PUV = posterior urethral valve; UUT = upper urinary tract; USG = urinary specific gravity; VCUG = voiding cystourethrogram; UT = urinary tract; RF = renal function; CIC = clean intermittent catheterisation; OAB = overactive bladder.

Table 6: Role of the paediatric urologist

<i>Diagnostic role</i>
<ul style="list-style-type: none">• Clinical examination• Ultrasound• Genitography• Cystoscopy• Diagnostic laparoscopy
<i>Therapeutic role</i>
<ul style="list-style-type: none">• Masculinising surgery• Feminising surgery• Gonadectomy

17.4.1 **Diagnosis**

17.4.1.1 *Clinical examination*

A good clinical examination in a neonate presenting with ambiguous genitalia is important. As well as a good description of the ambiguous genitalia, some detailed information should be given on palpability and localisation of the gonads. Information gathered by the various examinations described below should help the team to come to a final diagnosis.

Palpable gonad. It must be remembered that if it is possible to feel a gonad, it is almost certainly a testis; this clinical finding therefore virtually excludes 46XXDSD.

Medical photography can be useful but requires sensitivity and consent (3).

Phallus. The phallus should be measured. A cotton bud placed at the suprapubic base of the implant of the stretched phallus allows for a good measurement of phallic length.

Urogenital sinus opening. The opening of the urogenital sinus must be well evaluated. Is there only one opening visible? Can a hymenal ring be seen? What does the fusion of the labioscrotal folds look like; do the folds show rugae or some discolouration?

17.4.1.2 *Investigations*

Ultrasound can help to describe the palpated gonads or to detect non-palpated gonads. However, the sensitivity and specificity are not high. On ultrasound, the Müllerian structures can be evaluated. Is there a vagina? Are there some abdominal gonads? Is there a vaginal or utricular structure visible? (4,5).

Genitography can provide some more information on the urogenital sinus. How low or how high is the confluence? Is there any duplication of the vagina? How does the urethra relate to the vagina?

General anaesthesia. In some cases, further examinations under general anaesthesia can be helpful. On cystoscopy, the urogenital sinus can be evaluated and the level of confluence between the bladder neck and the bladder. Cystoscopy can also be used to evaluate the vagina or utriculus, e.g. the presence of a cervix at the top of the vagina can be important information.

Laparoscopy is necessary to obtain a final diagnosis on the presence of impalpable gonads and on the presence of Müllerian structures. If indicated, a gonadal biopsy can be performed (6,7).

17.5 **Management**

Referring to the consensus document (1,2), it is clear that the timing of surgery is much more controversial than it used to be.

The rationale for early surgery includes:

- Beneficial effects of oestrogen on infant tissue
- Avoiding complications from anatomical anomalies
- Minimising family distress
- Mitigating the risks of stigmatisation and gender-identity confusion (8).

However, adverse outcomes have led to recommendations to delay unnecessary surgery to an age when the patient can give informed consent. Surgery that alters appearance is not urgent. Early surgery should be reserved for those patients with high confluent urogenital tracts, girls with severely masculinised genitalia

and boys with undervirilised genitals. Vaginoplasty should be delayed until puberty and milder forms of masculinisation should not be treated surgically.

17.5.1 **Feminising surgery**

Clitororeduction. Reduction of an enlarged clitoris should be done with preservation of the neurovascular bundle. Clitoral surgery has been reported to have an adverse outcome on sexual function and clitoral surgery should therefore be limited to severely enlarged clitorises (9,10). Informed parental consent should be obtained. Although some techniques that conserve erectile tissue have been described, the long-term outcome is unknown (11).

Separation of the vagina and the urethra is preserved for high confluence anomalies. Many techniques for urogenital sinus repair have been described, but their outcome has not been evaluated prospectively (12, 13).

Vaginoplasty should be performed during the teenage years. Every technique (self dilatation, skin or bowel substitution) has its specific advantages and disadvantages (14). All carry a potential for scarring that would require further surgery before sexual function was possible.

Aesthetic refinements. The goals of genital surgery are to maximise anatomy to allow sexual function and romantic partnering. Aesthetics are important in this perspective. The reconstruction of minor labiae from an enlarged clitoral hood is an example of aesthetic refinement.

17.5.2 **Masculinising surgery**

Hormone therapy early in life is advocated by many doctors. The level of evidence is low for restoration of normal penile size.

Hypospadias surgery. See section on hypospadias (Chapter 6).

Excision of Mullerian structures. In the DSD patient assigned a male gender, Müllerian structures should be excised. There is no evidence about whether utricular cysts need to be excised.

Orchiopexy. See section on orchidopexy (Chapter 3).

Phalloplasty. The increasing experience of phalloplasty in the treatment of female to male transsexual patients has led to reports about the reliability and feasibility of this technique. It has therefore become available to treat severe penile inadequacy in DSD patients.

Aesthetic refinements. These include correction of penoscrotal transposition, scrotoplasty and insertion of testicular prostheses.

Gonadectomy. Germ cell malignancy only occurs in patients with DSD who have Y-chromosomal material. The highest risk is seen in patients with gonadal dysgenesis and in patients with partial androgen insensitivity with intra-abdominal gonads (LE: 2). Intra-abdominal gonads of high-risk patients should be removed at the time of diagnosis (GR: A) (15).

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18. POSTERIOR URETHRAL VALVES

18.1 Background

Posterior urethral valves (PUV) are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period. Despite optimal treatment, PUV in children may result in renal insufficiency in nearly 35% of cases. PUV are found in 1 in 1,250 in a population undergoing fetal ultrasound screening (1). An incidence of PUV of 1 in 5,000-12,500 live-births has been estimated (2, 3). In one report, up to 46% of fetuses with a PUV diagnosis were terminated (4), indicating a possible decrease in incidence.

18.2 Classification

18.2.1 Urethral valve

Despite recent attempts to introduce new classification terms, such as 'congenital obstructive posterior urethral membrane (COPUM)' (5), the original classification by Hugh Hampton Young remains the most commonly used (6).

Hampton Young described three categories: type I, type II and type III. However, today, only type I and type III are found to be obstructive. As type II seems to be more like a fold and not obstructive, it is no longer referred to as a valve. Hampton Young's descriptions of type I and II are as follows:

Type I (90-95%). 'In the most common type there is a ridge lying on the floor of the urethra, continuous with the verumontanum, which takes an anterior course and divides into two fork-like processes in the region of the bulbo-membranous junction. These processes are continued as thin membranous sheets, direct upward and

forward which may be attached to the urethra throughout its entire circumference. It is generally supposed that the valves have complete fusion anteriorly, leaving only an open channel at the posterior urethral wall. Yet the fusion of the valves anteriorly may not be complete in all cases, and this point a slight separation of the folds exist.' (6)

Type III. 'There is a third type of which has been found at different levels of the posterior urethra and which apparently bears no such relation to the verumontanum. This obstruction was attached to the entire circumference of the urethra, with a small opening in the centre.' (6).

The transverse membrane described has been attributed to incomplete dissolution from the urogenital portion of the cloacal membrane (7). The embryology of the urethral valves is poorly understood. The membrane may be an abnormal insertion of the mesonephric ducts into the fetal cloaca (8).

18.3 Diagnosis

An obstruction above the level of the urethra affects the whole urinary tract in varying degrees.

- The prostatic urethra is distended and the ejaculatory ducts may be dilated due to urinary reflux. The bladder neck is hypertrophied and rigid.
- The hypertrophied bladder occasionally has multiple diverticula.
- Nearly all valve patients have dilatation of both upper urinary tracts. This may be due to the valve itself and the high pressure in the bladder, or due to obstruction of the ureterovesical junction by the hypertrophied bladder.
- If there is secondary reflux, the affected kidney functions poorly in most cases.

During prenatal ultrasonography screening, bilateral hydroureteronephrosis and a distended bladder are suspicious signs of a urethral valve. If a dilated posterior urethra and a thick-walled bladder ('keyhole' sign) are seen, a PUV is likely. In the presence of increased echogenity of the kidney, dilatation of the urinary tract and oligohydramnion, the diagnosis of a PUV should strongly be considered.

A voiding cysturethrography (VCUG) confirms a PUV diagnosis. This study is essential whenever there is a question of an infravesical obstruction, as the urethral anatomy is well outlined during voiding. A secondary reflux is observed in at least 50% of patients with PUV (9). Reflux is consistently associated with renal dysplasia in patients with PUV. It is generally accepted that reflux in the renal units acts as a 'pressure pop-off valve', which would protect the other kidney, leading to a better prognosis (10). Other types of pop-off mechanism include bladder diverticula and urinary extravasation, with or without urinary ascites (11). However, in the long-term, a supposed protective effect did not show a significant difference compared to other patients with PUV (12,13).

Nuclear renography with split renal function is important to assess kidney function. Creatinine, blood urea nitrogen and electrolytes should be monitored closely during the first few days. A nadir creatinine of 80 $\mu\text{mol/L}$ is correlated with a better prognosis (14).

18.4 Treatment

18.4.1 Antenatal treatment

About 40-60% of PUV are discovered before birth (15). The intrauterine obstruction leads to a decreased urine output, which could result in an oligohydramnios. Amnion fluid is necessary for normal development of the lung and its absence may lead to pulmonary hypoplasia, causing a life-threatening problem. Intrauterine attempts have been made to treat a fetus with PUV.

As renal dysplasia is not reversible, it is important to identify those fetuses with good renal function. A sodium level below 100 mmol/L, a chloride value of < 90mmol/L and an osmolarity below 200 mOsm/L found in three fetal urine samples gained on three different days are associated with a better prognosis (16).

The placing of a vesicoamniotic shunt has a complication rate of 21-59%, dislocation of the shunt occurs in up to 44%, mortality lies between 33% and 43%, and renal insufficiency is above 50% (16-18). Although shunting is effective in reversing oligohydramnios, it makes no difference to the outcome and long-term results of patients with PUV (17,18).

18.4.2 Postnatal treatment

Bladder drainage. If a boy is born with suspected PUV, drainage of the bladder and, if possible, an immediate VCUG is necessary. A neonate can be catheterized with a 3.5-5 F catheter. A VCUG is performed to see if the diagnosis is correct and whether the catheter is within the bladder and not in the posterior urethra. An alternative option is to place a suprapubic catheter, perform a VCUG and leave the tube until the neonate is stable enough to perform an endoscopic incision or resection of the valve.

Valve ablation. When the medical situation of the neonate has stabilised and the creatinine level decreased, the

next step is to remove the intravesical obstruction. Small paediatric cystoscopes and resectoscopes are now available either to incise or to resect the valve at the 4-5, 7-8 or 12 o'clock position, or at all three positions, depending on the surgeon's preference. It is important to avoid extensive electrocoagulation as the most common complication of this procedure is stricture formation.

Vesicostomy. If the child is too small and/or too ill to undergo endoscopic surgery, a vesicostomy is used to drain the bladder temporarily. If initially a suprapubic tube has been inserted, this can be left in place for 6-12 weeks. Otherwise, a cutaneous vesicostomy provides an improvement or stabilisation of upper urinary tracts in over 90% of cases (19). Although there has been concern that a vesicostomy could decrease bladder compliance or capacity, so far there are no valid data to support these expectations (20-22).

High diversion. If bladder drainage is insufficient to drain the upper urinary tract, high urinary diversion should be considered. Diversion may be suitable if there are recurrent infections of the upper tract, no improvement in renal function and/or an increase in upper tract dilatation, despite adequate bladder drainage. The choice of urinary diversion depends on the surgeon's preference for high loop ureterostomy, ring ureterostomy, end ureterostomy or pyelostomy, with each technique having advantages and disadvantages (23-25). Reconstructive surgery should be delayed until the upper urinary tract has improved as much as can be expected.

Reflux is very common in PUV patients (up to 72%) and it is described bilaterally in up to 32% (26). High-grade reflux is mostly associated with a poor functioning kidney. However, early removal of the renal unit seems to be unnecessary, as long as it causes no problems. It may be necessary to augment the bladder and in this case the ureter may be used (27).

Life-long monitoring of these patients is mandatory, as bladder dysfunction is not uncommon and the delay in day- and night-time continence is a major problem (9, 14). Poor bladder sensation and compliance, detrusor instability and polyuria (especially at night) and their combination are responsible for bladder dysfunction. Between 10% and 47% of patients may develop end-stage renal failure (14, 28). Renal transplantation in these patients can be performed safely and effectively. Deterioration of the graft function is mainly related to lower urinary tract dysfunction (29,30).

18.5 References

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19. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

AGS	adrenogenital syndrome
ACTH	adrenocorticotrophic hormone
AMH	anti-Müllerian hormone
ARM	anorectal malformation
CAH	congenital adrenal hyperplasia
CIC	clean self-intermittent catheterisation
CNS	central nervous system
COPUM	congenital obstructive posterior urethral membrane
CRP	C-reactive protein
DDAVP	desmopressine
CT	computed tomography
DHTST	dihydrotestosterone
DMSA	dimercaptosuccinic acid
EMG	electromyography
ESR	erythrocyte sedimentation rate
ESWL	extracorporeal shockwave lithotripsy
FSH	follicle stimulating hormone
GnRH	gonadotrophin-releasing hormone
hCG	human chorionic gonadotrophin
IC	intermittent catheterisation
ICCS	International Children's Continence Society
IVU	intravenous urogram
LH	luteinising hormone
LHRH	luteinising hormone releasing hormone
LUTD	lower urinary tract dysfunction
LUT(S)	lower urinary tract (symptoms)
MRI	magnetic resonance imaging
NDS	neurogenic detrusor-sphincter dysfunction
OAB	overactive bladder
PNL	percutaneous litholapaxy
RCT	randomised controlled treatment trials
RN	reflux nephropathy
RNC	radionuclide cystography
RTA	renal tubular acidosis
Tc-MAG3 (99m)	technetium-99m mercaptoacetyltriglycine (MAG3)
TIP	tubularised incised urethral plate
TST	testosterone
UPJ	ureteropelvic junction
URS	ureterorenoscopy
US	ultrasound
UTIs	urinary tract infections
VCUG	voiding cystourethrography
VRR	vesicorenal reflux
VUR	vesicoureteral reflux
VUS	voiding urosonography

Conflict of interest

All members of the Paediatric Urology Guidelines working group have provided disclosure statements on all relationships that they have and that might be perceived to be a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.