EAU Guidelines on

Paediatric Urology

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1. INTRODUCTION

1.1 Aim

The European Association of Urology (EAU) Paediatric Urology Guidelines Panel has prepared these Guidelines with the aim of increasing the quality of care for children with urological conditions. This Guideline document is limited to several common clinical pathologies in paediatric urological practice, as covering the entire field of paediatric urology in a single guideline document is unattainable.

Most urological clinical problems in children are specialised and, in many ways, differ to those in adults. This publication intends to outline a practical and preliminary approach to paediatric urological conditions. Complex and rare conditions that require special care with experienced doctors should be referred to designated centres in which paediatric urology practice has been fully established and a multidisciplinary team is available.

Over time, paediatric urology has developed and matured, establishing 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 numerous 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.

It must be emphasised that, although clinical guidelines present the best evidence available to the experts, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients but rather help to focus decisions - also taking into account personal values and preferences/individual circumstances of children and their caregivers. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Paediatric Urology Guidelines Panel consists of an international group of clinicians with specific expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU Website: http://uroweb.org/guideline/paediatric-urology/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print. The Pocket Guidelines is an abridged version of the Guidelines, which may require consultation together with the full-text version. Various translated versions, along with several scientific publications, are also available [1-17]. All documents are accessible through the EAU website Uroweb: http://uroweb.org/guideline/paediatric-urology/.

An EAU Guidelines app for iOS and Android devices is also available, containing the Pocket Guidelines, interactive algorithms and calculators, clinical decision support tools, Guidelines cheat sheets, and links to the extended guidelines.

1.4 Publication history

The Paediatric Urology Guidelines were first published in 2001 [18]. This 2026 publication includes several updated chapters and sections, as detailed in the following section.

1.5 Summary of changes

The literature for the complete document has been assessed and updated, wherever relevant. Key changes in the 2026 publication:

- Section 12: Urinary tract infections in children
- Section 14: Management of monosymptomatic enuresis
- Section 16: Dilatation of the upper urinary tract (PUJ obstruction)
- Section 19: Ureterocele and ectopic ureter
- Section 22.2: Rare conditions in childhood: papillary tumours of the bladder in children and adolescents
- Section 22.3 Rare conditions in childhood: penile rare conditions
- Section 28 Foetal urology (new section).

2. METHODS

2.1 Introduction

These Guidelines were compiled based on current literature following a structured review. Databases covered by the searches included PubMed, Ovid, EMBASE, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. Application of a structured analysis of the literature was not possible in many conditions due to a lack of well-designed studies. The limited availability of large randomised controlled trials (RCTs) - also influenced by the fact that a considerable number of treatment options relate to surgical interventions on a large spectrum of various congenital problems - means this document is largely a consensus document. Clearly there is a need for continuous re-evaluation of the information presented in this document.

Recommendations within the Guidelines are developed by the Panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms that accompany each Guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which exists for the recommendation [19];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes; and;
5. the impact and certainty of patient values and preferences on the intervention.

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower-quality evidence and/or equivocal balance between benefit and harm and uncertainty or variability of patient preference [20].

Additional information can be found in the general Methodology section online at the EAU website: http://www.uroweb.org/guideline/.

A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Peer review

All chapters of the Paediatric Urology Guidelines were peer-reviewed in 2015.

3. PHIMOSIS AND OTHER ABNORMALITIES OF THE PENILE SKIN

The prepuce, or foreskin, of the penis is often a cause for concern to parents of young boys and physicians alike [21], with 10% seeking medical advice [22]. While there are some pathological abnormalities of the foreskin, these are in fact quite rare and must be discerned from physiological variations or developmental stages. In this chapter, we will highlight normal development, its variations and how to discern this from abnormal foreskin requiring treatment, and also provide various treatment options.

3.1 Terminology, epidemiology and pathophysiology

At birth, the foreskin can be retracted in 4% of boys. In 42% of neonates, the tip of the glans cannot be visualised. By the end of the first year of life, retraction of the foreskin behind the glandular corona is possible in approximately 50% of boys, increasing to 89% by the age of three years. Nonretractability of the foreskin can be a physiological phase that does not require treatment in the absence of symptoms, such as painful erections or balanitis.

Phimosis

In phimosis, the inability to retract the foreskin over the glans penis is due to a narrow ring in the prepuce. Several factors have been suggested to aid in the gradual dilation of this ring: histological changes in the prepuce, hormonal factors and stretching due to erections. While erections occur even antenatally, these may be insufficient to stretch the foreskin if it is relatively long, and therefore relative phimosis can be present for a prolonged period [23].

Epidemiological studies of the natural course of phimosis are difficult, as they are affected by treatment of a subgroup of subjects. Nonetheless, the incidence of phimosis is 9-20% in five- to 13-year-olds and just 1% in males aged 16 to 18 years [23, 24].

Preputial adhesions

Another cause of nonretractability of the prepuce are adhesions of the foreskin to the glans. This must be distinguished from phimosis. Usually when adhesions are present, partial retraction is possible and the meatus can be visualised [24]. Adhesions are a physiological phenomenon of variable duration, present in 63% of six- to seven-year-olds and 3% of 16- to 17-year-olds without phimosis [24]. Progressive separation of the inner prepuce from the glans is associated with build-up of epithelial debris (smegma) and aided by penile erections. During this process, smegma can accumulate into nodules that may be mistaken for cysts. When released from between the skin layers, smegma can resemble purulent discharge, especially when mixed with urine. Focal erythema may also occur temporarily. In the absence of other signs of infection, this should not be confused with balanitis.

Once adhesions between the glans and inner prepuce are resolved, ballooning of the foreskin may also occur during voiding, particularly if the opening of the prepuce is still relatively narrow. Ballooning is not a sign of obstructed voiding and uroflows have been shown to be normal with ballooning [25]. Therefore, ballooning may be a physiological phase, and it should only be considered a problem in case of (recurring) balanitis.

Paraphimosis

In paraphimosis, the foreskin has been retracted and cannot be brought back down to cover the glans of the penis. In children, it is most likely due to manipulation, with an incidence reported to be as low as 0.2% [22]. The risk of paraphimosis is higher if relative phimosis is present. The narrow ring in the retracted prepuce may constrict the shaft at the level of the sulcus, leading to oedema of the glans and retracted foreskin. Impaired perfusion may lead to necrosis of the prepuce and ultimately of the glans. Paraphimosis must be regarded as a medical emergency requiring urgent treatment [26].

Balanitis/balanoposthitis

Balanoposthitis can be defined as erythema and swelling of the glans (balanitis) and/or foreskin (posthitis), with discharge of pus. It should not be confused with focal irritation due to retention of droplets of urine under the foreskin. Balanoposthitis may be seen in 6% of uncircumcised boys [22, 27].

Balanitis xerotica obliterans

Balanitis xerotica obliterans (BXO) is a non-painful chronic inflammatory disease that may affect the glans, foreskin, meatus and urethra. As such, it is a genital form of lichen sclerosus et atrophicus [23]. Balanitis xerotica obliterans may lead to scarring, phimosis and urethral outflow problems. Histological analysis of the prepuces of children and adolescents undergoing circumcision for medical reasons shows signs of BXO in 35%-53% [28]; in boys younger than ten years, this is 17% [29, 30].

Inconspicuous penis

The following are various types of concealed or inconspicuous penis, which should be differentiated from truly small penis such as micropenis, with abnormal size of the corporeal bodies or even aphallia:

- Buried penis and megaprepuce are congenital anomalies in which the skin is folded abnormally around the shaft. The opening of the prepuce can be narrow, prohibiting retraction similar to regular phimosis, but may also be normal. Buried penis can occasionally be due to abnormal prepubic fat distribution, which may be self-limiting with growth or weight loss.
- In webbed penis, the penoscrotal angle is abnormal due to the scrotum being attached high on the ventral side of the shaft.
- Trapped penis is an iatrogenic form of buried penis that may be caused by resection of too much skin during circumcision [31].

3.2 Classification and diagnostic evaluation

To determine which cases require treatment, phimosis should be divided into a physiological and pathological type. Physiological phimosis is most likely to resolve over time without intervention, whereas pathological phimosis may not.

In physiological phimosis, there is no sign of scarring and, upon retraction, the inner prepuce is seen bulging outward from the narrow ring in the prepuce ('pouting'). In pathological or secondary phimosis, there is scarring; the narrow ring in the prepuce is fibrous, often white and thickened; and the inner layer of the prepuce is not seen coming out [32]. Balanitis xerotica obliterans is a special form of pathological phimosis.

The diagnosis of adhesions, phimosis and paraphimosis is made by physical examination alone and can differentiate between physiological variations or pathological abnormalities. If the prepuce is not retractable, or only partly retractable, and shows a constrictive ring upon retraction back over the glans penis, a disproportion between the width of the foreskin and the diameter of the glans penis must be assumed. In addition to the constricted foreskin, the inner prepuce may be adherend to the glans and/or frenulum breve.

Balanitis xerotica obliterans remains a histopathological diagnosis, as clinically discerning BXO from simple pathological phimosis by may be difficult, particularly to the untrained eye. Histopathological examination of resected foreskin is warranted due to the consequences of this diagnosis with regards to follow-up [33, 34].

In buried penis, the shaft itself appears shorter upon inspection but is of normal size upon palpation, hence the name. In megaprepuce, the shaft may have a normal appearance, or it may resemble buried penis. The diagnosis is made based on the aspect of the penis during voiding. When the enlarged space between shaft and inner prepuce fills up with urine during voiding, this causes the entire penis to swell. Megaprepuce can be discerned from regular phimosis, in which only the tip of the penis may demonstrate ballooning. It may be helpful if caregivers show a photo or even video of the aspect of the penis during voiding.

3.3 Management

Hygiene

The foreskin should not be retracted for cleaning until this can be done easily. It should be stressed to parents/caregivers that forced retraction of a narrow foreskin may cause scar formation, resulting in secondary pathological phimosis [35]. Care should be taken to reduce the foreskin back down over the glans to prevent paraphimosis. Once the foreskin is retractable, this can be done regularly during bathing and becomes necessary for hygienic reasons starting in puberty. The production of smegma appears to increase at puberty, coinciding with the age at which most boys can retract their foreskin [32].

Conservative/medical management

Physiological phimosis and adhesions do not require treatment unless there are accompanying urogenital abnormalities. Conservative medical treatment is a valid option for primary pathological phimosis. Class 4 corticosteroid therapies were more effective over placebo and manual stretching [36]. Topical corticoid (0.05-0.1%) can be administered twice a day over a period of four to eight weeks with a success rate of >80% [36-39]. A publication showed that lower class corticosteroids may be almost equally effective [40]. A recurrence rate of up to 17% can be expected [41]. Effectivity of topical corticosteroids is likely to be influenced by correct application, which must be directly onto the narrow ring under gentle retraction. Similarly, after finishing the corticosteroid treatment, recurrence should be prevented by continuing daily retraction of the prepuce [42]. While all types of phimoses may respond to corticosteroid treatment, the success rate may be lower in pathological phimosis. If BXO is suspected, consultation with a dermatologist should be considered [43].

Corticosteroid treatment has no systemic side effects, and mean blood cortisol levels are not significantly different from an untreated group of patients [44]. The hypothalamic-pituitary-adrenal axis was not influenced by local corticoid treatment [45]. However, if treatment is continued for too long or too much product is used, this may cause focal atrophy and vulnerability of the skin. In general, cream may be associated with dryness and irritation, due to the nature of the product compared to ointment. Adhesion of the foreskin to the glans does not respond to corticosteroid treatment [37].

Operative management

Circumcision for nonmedical reasons, such as routine circumcision for cultural, religious or hygienic considerations, is not discussed in this chapter.

Medical indications for surgical intervention for phimosis are recurrent balanoposthitis or symptomatic therapy-resistant phimosis. Simple ballooning of the foreskin during micturition is not an indication for surgery *per se*. Several indications for circumcision in the absence of symptomatic phimosis have been proposed. In boys with increased risk of urinary tract infections (UTIs) due to congenital upper tract abnormalities, circumcision may be performed to reduce the risk of UTIs [46-49]. Male circumcision significantly reduces the bacterial colonisation of the glans penis with regard to both non-uropathogenic and uropathogenic bacteria [50]. However, resolution of phimosis by corticosteroid treatment may have similar results, as it was also associated with substantial reduction in recurrent UTI in uncircumcised infants [51]. (See Chapter 12, Urinary tract infections in children, and Chapter 17, Vesicoureteric reflux).

Routine neonatal circumcision to prevent penile carcinoma is not indicated. A meta-analysis could not find any risk in uncircumcised patients without a history of phimosis [52].

The type of operative treatment of phimosis in children is dependent on the caregivers' preferences and can be preputioplasty or circumcision. In preputioplasty, the objective is to preserve the prepuce while achieving a wider foreskin circumference with full retractability. Several surgical techniques have been described to achieve this goal: dorsal incision, partial circumcision, and trident preputioplasty, which combines two Z-plasties and Y-plasty [53, 54]. The main disadvantage of preputioplasty is the inherent potential for recurrence of phimosis [55].

In circumcision, the prepuce is resected completely. Contraindications for circumcision are: an acute local infection and congenital anomalies of the penis, particularly hypospadias; buried penis and megaprepuce; epispadias; and congenital penile curvature, as the foreskin may be required for a reconstructive procedure [56, 57].

When surgically correcting phimosis, additional issues should be addressed during the same session: adhesions are released, an associated frenulum breve is corrected by frenulotomy, and the meatus is calibrated with meatoplasty added if necessary.

Paraphimosis treatment

Treatment of paraphimosis consists of manual compression of the oedematous tissue with a subsequent attempt to retract the tightened foreskin over the glans penis [58, 59]. If this manoeuvre fails, a dorsal incision of the constrictive ring is required. Following acute redressing of the foreskin, additional treatment is recommended to correct any anomalies that increase the chance of recurrence. Patients should be counselled regarding prevention of paraphimosis by correctly redressing their foreskin after retraction.

3.4 Complications

Complications following circumcision vary and have been reported in between 0-30% of all circumcisions [60]. Hung *et al.* found 2.9% complications in non-neonates during a five-year follow-up period; 2.2% were early (within 30 days after circumcision). Nonhealing wounds, haemorrhage, wound infection, meatal stenosis, redundant skin, non-satisfying cosmetic appearance and trapped penis all may occur [61]. The incidence of post-circumcision meatal stenosis is higher in boys with confirmed BXO compared to those who underwent circumcision for phimosis without BXO (20% vs. 6%) [33]. Overall, the risk of complications appears low when done by professionals in a medical setting.

3.5 Follow-up

Any preputial surgery requires early follow-up of four to six weeks after surgery. In case of BXO, prolonged follow-up is warranted and may involve a dermatologist. Balanitis xerotica obliterans is associated with meatal pathology (stenosis) after circumcision in up to 20% of boys [30, 62, 63].

3.6 Summary of evidence and recommendations for the management of phimosis

Summary of evidence	LE
Nonretractability of the foreskin, preputial adhesions and ballooning may be a physiological phase before puberty and do not require treatment in the absence of symptoms.	3
Forced retraction of a narrow foreskin should be avoided to prevent scar formation, which may result in secondary pathological phimosis.	3
Conservative treatment of phimosis with topical corticosteroids (ointment or cream) has a high success rate, but surgical treatment may be considered if preferred by caregivers or patients.	1b
Balanitis xerotica obliterans warrants prolonged follow-up due to risk of meatal stenosis or urethral involvement.	2

Recommendations	Strength rating
Offer topical corticosteroids (ointment or cream) as first-line treatment in symptomatic phimosis.	Strong
Consider surgical intervention (if patient/caregivers prefer) for symptomatic phimosis.	Strong
Offer circumcision in case of Balanitis xerotica obliterans (BXO) or phimosis refractory to treatment.	Strong
Offer treatment for asymptomatic phimosis in infants with a risk of recurrent urinary tract infection due to upper urinary tract abnormalities (vesicoureteral reflux or posterior urethral valves).	Strong
Inform patients about the risk of meatal stenosis in BXO.	Strong
Await spontaneous resolution of asymptomatic preputial adhesions before puberty.	Weak
Treat paraphimosis by manual reposition and, if this fails, proceed to surgery.	Strong
Do not perform simple circumcision if phimosis is associated with other penile anomalies such as buried penis, congenital penile curvature, epispadias or hypospadias.	Strong

4. MANAGEMENT OF UNDESCENDED TESTES

4.1 Background

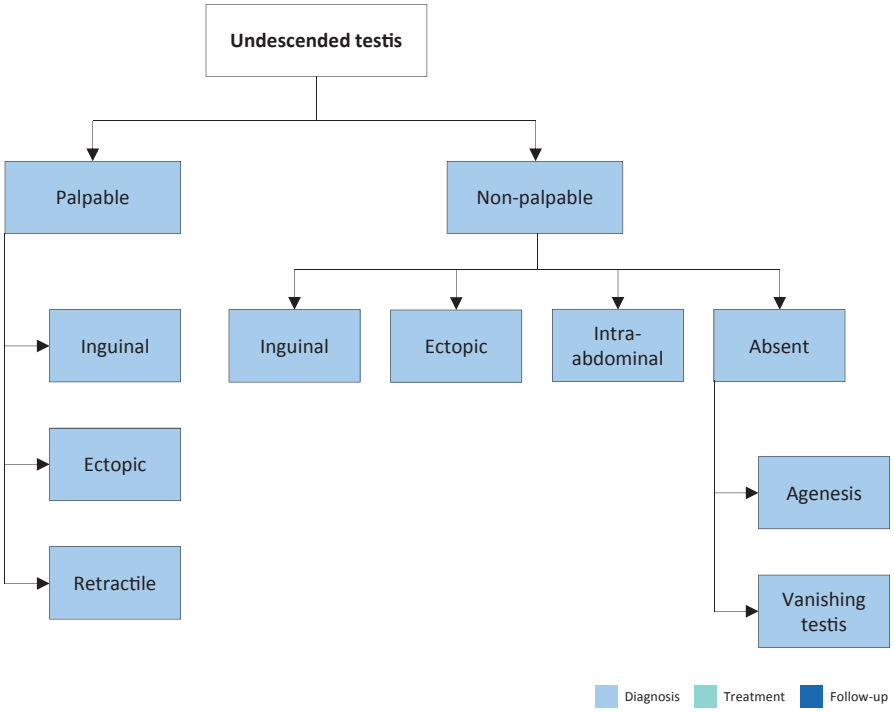
The term cryptorchidism is most often used synonymously with undescended testes and is one of the most common congenital malformations of male neonates. The incidence varies and depends on gestational age, affecting 1.0-4.6% of full-term and 1.1-45% of preterm neonates. Following spontaneous descent within the first months of life, nearly 1.0% of all full-term male infants still have undescended testes at one year of age [64]. Cryptorchidism can occur bilaterally in up to 30% of cases [65]. In newborn cases with nonpalpable or undescended testes on both sides and any sign of disorders of sex development (DSDs), such as concomitant hypospadias, endocrinological and genetic evaluation is required to assess for any form of DSD (see Chapter 20, Disorders/differences of sex development) [66]. Children with abdominal wall defects such as gastroschisis and omphalocele were shown to have higher rates of cryptorchidism [67], with a higher atrophy rate overall [68]. Cryptorchidism is associated with an increased risk of impaired fertility and testicular cancer, not limited to congenital cases. Structural abnormalities are often found in the affected testicles, and they are typically smaller in size [69]. While congenital cryptorchidism increases the risk of infertility, ascending testes can also affect fertility potential, though to a lesser extent [70-73]. Histological changes in acquired cases mirror those seen in congenital cryptorchidism, highlighting the need for careful management to reduce fertility risks [70, 71, 73, 74].

4.2 Classification

The most useful classification of undescended testes is distinguishing into palpable and nonpalpable testes, and clinical management is decided by the location and presence of the testes (see Figure 1). Approximately 80% of all undescended testes are palpable [75]. Acquired cryptorchidism is a condition where testes that were previously in a scrotal location ascend secondarily. This condition can be caused by entrapment after inguinal surgery or spontaneously referred to as ascending testes. The prevalence rates of ascending testis were found to range between 1 and 2% in a population study [76].

Palpable testes include true undescended testes in an inguinal or ectopic location. Nonpalpable testes include intra-abdominal, absent, and sometimes also some inguinal or ectopic testes. Some nonpalpable testes can become palpable under general anaesthesia.

Figure 1: Classification of undescended testes



4.2.1 Palpable testes

Undescended testes

A true undescended testis is on its normal path of descent but is halted on its way down to the scrotum. Depending on the location, the testes may or may not be palpable, as in the case of testes arrested in the inguinal canal.

Ectopic testes

If the position of a testis is outside its normal path of descent and outside the scrotum, the testis is considered ectopic. The most common aberrant position is in the superficial inguinal pouch. In some case, an ectopic testis can be identified in a femoral, perineal, pubic, penile or even contralateral position. Usually, there is no possibility for an ectopic testis to descend spontaneously to the correct position. It therefore requires surgical intervention. In addition, an ectopic testis might not be palpable due to its position. Additionally, there are cases reported of patients born with supernumerary testes as a rare phenomenon [77].

Retractile testes

Retractile testes have completed their descent into a proper scrotal position but can be found again in a suprascrotal position along the path of their normal descent. This is due to an overactive cremasteric reflex [78]. Retractile testes can be easily manipulated down to the scrotum and remain there at least temporarily. They are typically normal in size and consistency. As retractile testes carry a higher risk of secondary ascent of up to 33%, yearly controls until puberty are recommended [79].

4.2.2 Nonpalpable testes

Among the 20% of nonpalpable testes, 50-60% are intra-abdominal, canalicular or peeping (changing location between high inguinal position and inside the internal inguinal ring). The remaining 20% are absent and 30% are atrophic or rudimentary.

Intra-abdominal testes

Intra-abdominal testes can be in different positions, with most of them being found close to the internal inguinal ring. However, possible locations include the kidney, anterior abdominal wall and retrovesical space. In the case of an open internal inguinal ring, the testis may be peeping into the inguinal canal.

Absent testes

Monorchidism can be identified in up to 4% of boys with undescended testes, and anorchidism (bilateral absence) in <1%. Possible pathogenic mechanisms include testicular agenesis and atrophy after intrauterine torsion, which is referred to as ‘vanishing testes’ [80].

4.3 Diagnostic evaluation

History taking and physical examination are key in evaluating boys with undescended testes. Localisation studies using various imaging modalities are usually without any additional benefit.

4.3.1 History

Caregivers should be asked for maternal and paternal risk factors, including hormonal exposure and genetic or hormonal disorders. If the child has a history of previously descended testes, this might be suggestive of retractile testes or secondary testicular ascent [81]. A history of acute scrotal pain and swelling can be suggestive of a missed testicular torsion. Prior inguinal surgery is indicative of secondary undescended testes due to entrapment.

4.3.2 Physical examination

An undescended testis is pursued by carefully advancing the examining fingers along the inguinal canal towards the pubis region, perhaps with the help of lubricant. A possible inguinal testis can be felt to bounce under the fingers [82]. A nonpalpable testis in the supine position may become palpable with positional manoeuvres (e.g. frog-legged or cross-legged), which is a sign of a retractile testis. If no testis can be identified along the normal path of descent, possible ectopic locations must be considered.

In the event of unilateral nonpalpable testis, the contralateral testis must be examined. The size and location of the contralateral testis can have important prognostic implications. Any compensatory hypertrophy could suggest testicular absence or atrophy [83]. Nevertheless, this does not preclude surgical exploration, since the sign of compensatory hypertrophy is not specific enough [84-86].

In the case of bilateral nonpalpable testes or any evidence or sign of disorders/differences of sex development (DSDs) - such as genital ambiguity - or scrotal hyperpigmentation, further evaluation including endocrinological and genetic assessment becomes mandatory [87].

4.3.3 Imaging studies

Imaging studies cannot determine with certainty whether or not a testis is present [88]. Ultrasound (US) lacks the diagnostic sensitivity and specificity to detect the testis confidently or to establish the absence or presence of an intra-abdominal testis [89]. Consequently, the use of various imaging modalities for undescended testes, such as US or magnetic resonance imaging (MRI) [90], is limited and only recommended in specific and selected clinical scenarios (e.g. identification of Müllerian structures in cases with suspicion of DSDs) [89].

4.4 Management

Treatment should be started at the age of six months, since after that age, undescended testes rarely descend [91]. Any type of treatment leading to a scrotally positioned testis should be finished by 12 months, or 18 months at the latest, because histological examination of undescended testes at that age has already revealed a progressive loss of germ cells and Leydig cells [92]. The early timing of treatment is also driven by the final adult results on spermatogenesis and hormone production, as well as on the risk of tumour development [93].

4.4.1 Medical therapy

Unfortunately, most of the studies on hormonal treatment have been of poor quality, with heterogeneous and mixed patient populations, testis location, schedules and dosages of hormonal administration. Additionally, long-term data are almost completely lacking.

Short-term side effects of hormonal treatment include increased scrotal erythema and pigmentation and induction of pubic hair and penile growth. Some boys experience pain after intramuscular injection of human chorionic gonadotropin (hCG). All of these tend to regress after treatment cessation [94, 95].

Although many systemic side effects are temporary and typically resolve within six months, there are documented impacts on the testes, such as interstitial bleeding and germ cell apoptosis, which have been linked to a reduction in testicular volume later in adulthood [96, 97].

4.4.1.a Medical therapy for testicular descent

Hormonal therapy using hCG or gonadotropin-releasing hormone (GnRH) is based on the hormonal dependence of testicular descent but has a limited success rate of only 20% [98]. However, it must be noted that nearly 20% of these descended testes have the risk of reascending later [99]. In general, success rates depend on testicular location. The higher the testis is located prior to therapy, the lower the success rate, suggesting that testicular position is an important determinant of success [94]. Some authors recommend combined hCG-GnRH

treatment. Unfortunately, this type of treatment is poorly documented, and the treatment groups were diverse. Some studies reported successful descent in up to 38% of nonresponders to monotherapy [100]. A recent meta-analysis concludes that there is no consistent evidence to support hormone treatment alone in the management of undescended testes [69].

4.4.1.b Medical therapy for fertility potential

Hormonal treatment may improve fertility indices [101, 102] and therefore serve as an additional tool to orchidopexy. A longitudinal study on boys undergoing hormone therapy (hCG) with or without surgery showed that patients with hormone therapy had better sperm quality compared to patients undergoing surgery alone or no treatment at all [103]. There is no difference in treatment with GnRH before (neoadjuvant) or after (adjuvant) orchidopexy in terms of increasing fertility index, which may be a predictor for fertility later in life [104].

Identification of specific subgroups of boys with undescended testes who would benefit from using hormones is challenging. Since these important data on specific groups as well as additional support on the long-term effects are still lacking, the Nordic consensus does not recommend hormonal therapy [105].

As endocrine treatment may improve fertility index, the consensus of this Panel is to recommend endocrine treatment with GnRH analogues for boys with bilateral undescended testes to try to preserve fertility potential (LE: 4).

*4.4.2 **Surgical therapy***

If a testis has not concluded its descent at the age of six months (corrected for gestational age), and because spontaneous testicular descent is unlikely to occur after that age, surgery should be performed within the subsequent year [93]. A systematic review and meta-analysis comparing outcomes of orchidopexy before and after one year of age found no difference in atrophy rate, however, early orchidopexy was associated with greater testicular volume and more spermatogonia per tubule (fertility index) as possible markers for improved fertility potential [106]. These findings underscore the importance of early orchidopexy between the ages of six and twelve months (18 months at the latest) [91]. But despite early and successful orchiopexy within the first year of life, up to 25% of boys with non-syndromic undescended testes may be at risk for infertility based on hormonal and histological data as a series on 333 boys showed [107]. This is especially true for bilateral cases, but in addition in approximately 5% of unilateral cases, reduced numbers of germ cells were detected in testicular biopsies as well [107].

4.4.2.a Palpable testes

Surgery for palpable testes includes orchidofunicolysis and orchidopexy, either via an inguinal or scrotal approach, which are described in the following section.

*4.4.2.a.1 **Inguinal orchidopexy***

Inguinal orchidopexy is a widely used technique with a high success rate of up to 92% (definition of success: correct scrotal position) [108]. Important steps include mobilisation of the testis and spermatic cord to the level of the internal inguinal ring, with dissection and division of all cremasteric fibres, to prevent secondary retraction and detachment of the gubernaculum testis. The patent processus vaginalis must be dissected off the spermatic cord proximally at the level of the internal ring, because an unidentified or inadequately repaired patent processus vaginalis is an important factor leading to failure of orchidopexy [109].

At this moment, the size of the testis can be measured and the connection of the epididymis to the testis can be judged and described in the protocol. Some boys have a significant dissociation between testis and epididymis, which is associated with a lower testicular volume [110]. Finally, the mobilised testicle must be placed in a subdartos pouch within the hemiscrotum without any tension. If the length achieved using the above-mentioned technique is still inadequate, the Prentiss manoeuvre, which consists of dividing the inferior epigastric vessels and transposing the spermatic cord medially to provide a straight course to the scrotum, might be an option [111]. With regard to fixation sutures, if required, they should be made between the tunica vaginalis and the dartos musculature [112]. A recent systematic review and meta-analysis showed no benefit of performing a transparenchymal fixation suture in standard orchidopexy [113]. Lymph drainage of a testis that has undergone surgery for orchidopexy may have changed from high retroperitoneal drainage to iliac and inguinal drainage, which might become important in the event of later malignancy [114].

4.4.2.a.2 *Scrotal orchidopexy*

Low-positioned, palpable undescended testis can be fixed through a scrotal incision including division of the gubernaculum. The processus vaginalis must be probed to check for patency [115]. Otherwise, fixation in the scrotum is carried out correspondingly to the inguinal approach. In up to 20% of cases, an inguinal incision will be required to correct an associated patent processus vaginalis [116]. Any testicular or epididymal appendages can be easily identified and removed. A systematic review shows that the overall success rates (definition of success rates: correct scrotal position) ranged from 88 to 100%, with rates of recurrence and postoperative testicular atrophy or hypotrophy <1% [117]. Another systematic review and meta-analysis revealed similar outcome data regarding postoperative complications, including wound infection, testicular atrophy, testicular reascent and hernia for palpable low-positioned undescended testes. The only significant difference was the shorter operative time [118]. Overall, it can be concluded that scrotal orchidopexy appears to be a good surgical alternative for low lying testis [119-121].

4.4.2.b Nonpalpable testes

For nonpalpable testes, surgery must clearly determine whether a testis is present or not [122]. If a testis is found, the decision must be made to bring the testis down to the scrotum or to remove it. An important step in surgery is a thorough re-examination once the boy is under general anaesthesia, since a previously non-palpable testis might be identifiable and subsequently change the surgical approach to standard inguinal orchidopexy, as described previously. The optimal approach to locate an intra-abdominal testis is diagnostic laparoscopy [123]. Subsequent removal or orchidolysis and orchidopexy can be carried out laparoscopically [124]. If an ipsilateral scrotal nubbin is suspected, and contralateral compensatory testicular hypertrophy is present, a scrotal incision with removal of the nubbin, thus confirming the vanishing testis, is an option avoiding the need for laparoscopy [125].

During laparoscopy for nonpalpable testes, possible anatomical findings include spermatic vessels entering the inguinal canal (40%), an intra-abdominal (40%) or peeping (10%) testis, or blind-ending spermatic vessels confirming vanishing testis (10%) [126].

In case of a vanishing testis, the procedure is finished once blind-ending spermatic vessels are clearly identified. If the vessels enter the inguinal canal, one may find an atrophic testis upon inguinal exploration or a healthy testis that needs to undergo standard orchidopexy [127]. If a nubbin is found during inguinal exploration, it should be resected [69, 128]. A peeping testis can be placed down in the scrotum laparoscopically or by means of an inguinal incision [129]. Placement of an intra-abdominal testis can sometimes be a surgical challenge. Usually, testes lying high above the internal inguinal ring may not reach the scrotum with a single surgery [130]. Under such circumstances, a staged orchidopexy may be an option [131] (see Figure 2).

If a staged procedure is required, the most common techniques described in the literature are the Fowler-Stephens procedure and the Shehata technique for intra-abdominal testes [132]. Overall, laparoscopic orchidopexy for intraabdominal testes is associated with a slightly higher atrophy rate and rate of retraction compared to the conventional inguinal approach, especially if a staged approach is required [69].

The Fowler-Stephens technique involves proximal cutting and transection of the testicular vessels, with conservation of the collateral arterial blood supply, via the deferential artery and cremasteric vessels. A modification with low spermatic vessel ligation has gained popularity, allowing blood supply from the testicular artery to the deferential artery. An additional advantage is the position of the peritoneal incision, leading to a longer structure, to ease later scrotal placement [133]. Due to the nature of these approaches, the testis is at risk of hypotrophy or atrophy if the collateral blood supply is insufficient [134]. One- and two-stage FS have similar rates of retraction, whereas one-step procedures might have a higher rate of testicular atrophy [69]. The advantages of two-stage orchidopexy, with the second part usually done six months after the first, are to allow for development of collateral blood supply and to create greater testicular mobility [135]. In addition, preservation of the gubernaculum may also decrease the chance of testicular atrophy [136].

An alternative option to approach intra-abdominal testes is the Shehata technique. The first step involves spermatic vessel traction instead of vessel division [132]. A multicentre comparative study and a recent systematic review and meta-analysis show that both Fowler-Stephens orchidopexy and the traction technique are comparable in terms of postintervention testicular atrophy, testicular retraction/ascent [137, 138]. However, the mean operative time is significantly less with FS technique in Stage I laparoscopic orchidopexy [139]. As several studies have validated the safety and similar success rate of these approaches, it is up to the surgeon's preference and experience to decide which approach to use.

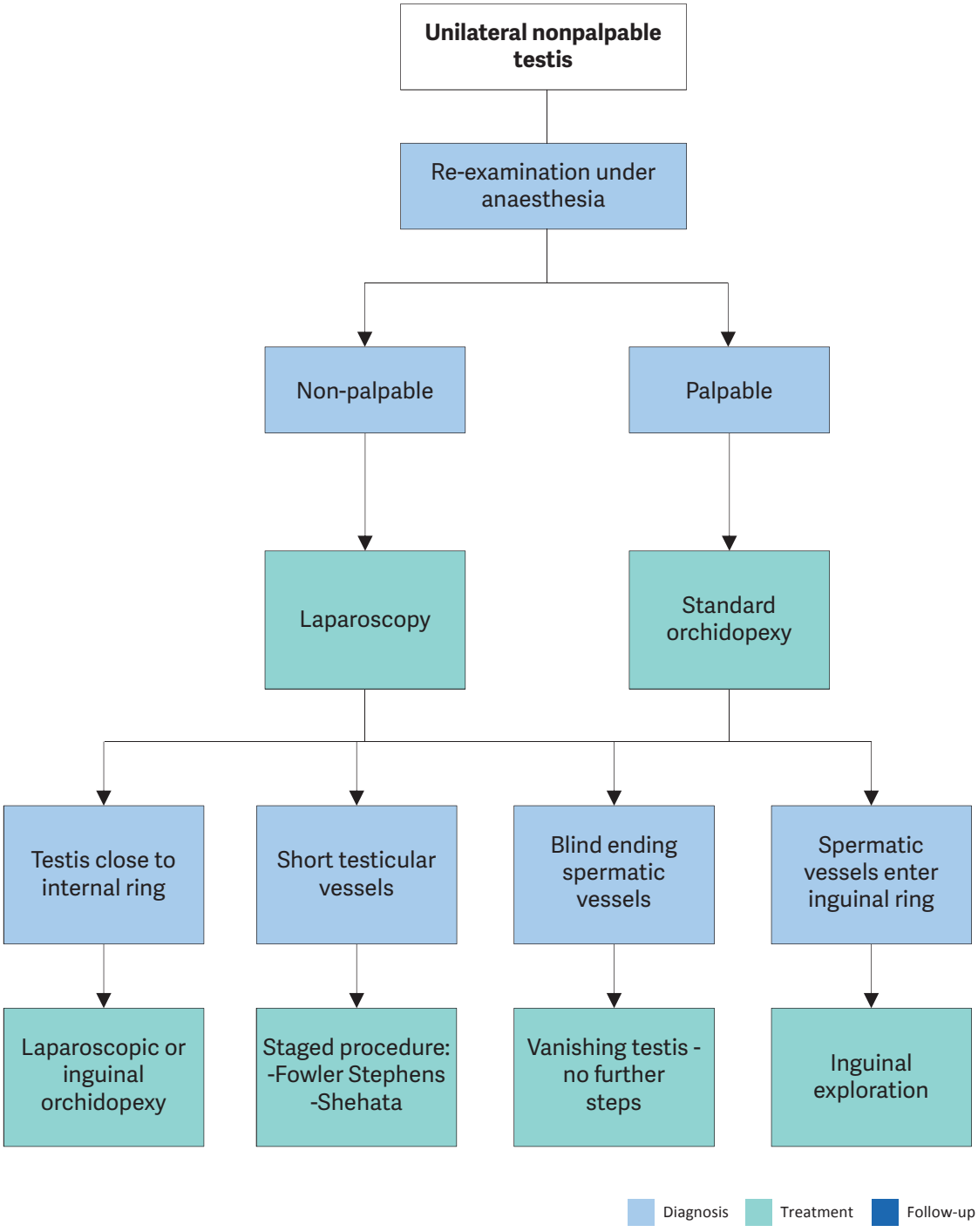
4.4.2.c Complications of surgical therapy

Surgical complications are usually uncommon, including testicular atrophy. A systematic review revealed an overall atrophy rate for primary orchidopexy of 1.83%, 28.1% for a one-stage Fowler-Stephens procedure, and 8.2% for the two-stage approach [140]. Other rare complications include testicular ascent and vas deferens injury, in addition to local wound infection, dehiscence and haematoma.

4.4.2.d Surgical therapy for undescended testes after puberty

The Panel consensus recommends orchidopexy in palpable undescended testes and orchiectomy in post-pubertal boys with an intraabdominal testis and a normal contralateral testis in a scrotal position. For adult recommendations, see the EAU Guidelines on Testicular Cancer [137, 138].

Figure 2: Treatment of unilateral nonpalpable undescended testes



4.5 Undescended testes and fertility

The association of undescended testes with compromised fertility [143] is discussed extensively in the literature and seems to be a result of multiple factors, including germ cell loss, impaired germ cell maturation [144], Leydig cell diminution and testicular fibrosis [145].

Although boys with one undescended testis have a lower fertility rate, they have the same paternity rate as those with bilateral descended testes. Boys with bilateral undescended testes suffer both: lower fertility and paternity rates. Fertility rate is the number of offspring born per mating pair, individual or population, whereas paternity reflects the actual potential of fatherhood [146]. The age at which surgical intervention for an undescended testis occurs seems to be an important predictive factor for fertility later in life. Endocrinological studies revealed higher inhibin-B and lower follicle-stimulating hormone (FSH) levels in men who underwent orchidopexy at two years of age compared to individuals who had surgery later, which is indicative of a benefit of earlier orchidopexy [147, 148]. In addition, others demonstrated a relation between undescended testes and increased loss of germ cells and Leydig cells, which is also suggestive of timely orchidopexy being a significant factor for fertility preservation [149]. Outcome studies for untreated bilateral undescended testes revealed that 100% are oligospermic and 75% azoospermic. Among those successfully treated for bilateral undescended testes, 75% remain oligospermic and 42% azoospermic [145].

In summary, early surgical correction of undescended testes is highly recommended before 12 months of age, and by 18 months at the latest, for preservation of fertility potential [92].

4.6 Undescended testes and malignancy

Boys who are treated for an undescended testis have an increased risk of developing testicular malignancy [141]. Screening and self-examination both during and after puberty is therefore recommended [150]. A Swedish study, with a cohort of nearly 17,000 men (56 developed a testicular tumour) who were treated surgically for undescended testes and followed for 210,000 person-years, showed that management of undescended testes before the onset of puberty decreased the risk of testicular cancer. The relative risk of testicular cancer among those who underwent orchidopexy before 13 years of age was 2.2 compared to the Swedish general population; this increased to 5.4 for those treated after 13 years of age [151]. A systematic review and meta-analysis of the literature have also concluded that prepubertal orchidopexy may reduce the risk of testicular cancer, and that early surgical intervention is indicated in boys with undescended testes [152].

4.7 Summary of evidence and recommendations for the management of undescended testes

Summary of evidence	LE
A failed or delayed orchidopexy may increase the risk of testicular malignancy later in life.	2a
Early treatment reduces the risks of impaired fertility and testicular cancer.	2a
In unilateral undescended testis, fertility rate is reduced whereas paternity rate is not.	1b
In bilateral undescended testes, both fertility and paternity rates are impaired.	1b
The treatment of choice for undescended testis is surgical positioning into the scrotum.	1b
The palpable testis is usually treated surgically using an inguinal approach.	2b
The nonpalpable testis should be approached laparoscopically.	2b

Recommendations	Strength rating
Do not offer medical or surgical treatment for retractile testes but undertake close follow-up on a regular basis until puberty.	Strong
Do not offer hormonal therapy in unilateral undescended testes for testicular descent only.	Strong
Offer endocrine treatment in cases of bilateral undescended testes to preserve future fertility potential.	Weak
Perform surgical orchidofunicolysis and orchidopexy before the age of 12 months, and by 18 months at the latest.	Strong
Perform an endocrinological workup in the setting of bilateral nonpalpable testes.	Strong
Perform an exam under anaesthesia and subsequent diagnostic laparoscopy to locate an intra-abdominal testicle.	Strong
Inform the patient/caregivers of the increased risk of malignancy with an undescended testis increasing with the age at orchidopexy.	Weak

5. TESTICULAR TUMOURS IN PREPUBERTAL BOYS

5.1 Epidemiology and pathophysiology

Testicular tumours constitute approximately 1-2% of all paediatric solid tumours [153]. Testicular tumours originate from various cell types within the testis, with the specific cell of origin determining the tumour's phenotype. This document addresses prepubertal testicular tumours. For information regarding postpubertal testicular tumours, please refer to the EAU Guidelines on Testicular Cancer [142].

In prepubertal boys, testicular tumours differ significantly from those in adolescent and adult men: they have a lower incidence (0.5 to 2 per 100,000 children, with a peak incidence between ages 0 and 4); they have a different histologic distribution; they are mostly benign (60-75%) [153-158]; and intratubular neoplasia (TIN) is practically non-existent in children [159-164]. Testicular tumours can generally be classified as germ cell tumours (GCT) or stromal tumours. Among prepubertal intra-testicular tumours, GCT account for 71-90%, of which approximately 40% to 50% are teratomas, with reports of immature teratomas in this age group [160, 165]. Epidermoid cysts comprise up to 10% to 15% of all GCTs and are consistently benign [161]. Malignant GCTs, predominantly yolk-sac tumours, range from 8% to 30% in frequency.

One specific tumour type is gonadoblastoma, which contains germ cell and stromal cell tumour types and will occur almost exclusively in the setting of DSD [166].

For differential diagnosis of a scrotal mass, paratesticular tumours should be excluded, such as benign types (leiomyoma, fibroma, lipoma, hemangioma, cystic lymphangioma, and lipoblastoma), in addition to the malignant tumours such as a rhabdomyosarcoma [166-168].

5.2 Clinical presentation

Clinical presentation is a painless scrotal mass in more than 90% of the patients, detected by the caregiver, physician or the patient himself. A history of a trauma, pain or hernia is rare. A hydrocele can be found in 15-50% of patients [151, 163]. In boys with early onset of puberty (e.g. early penile and prepubic hair growth) as well as high testosterone and low gonadotropin levels, a Leydig cell tumour should be excluded [164].

5.3 Evaluation

Ultrasound

To confirm the diagnosis, a high-resolution US examination (7.5-12.5MHz), preferably a Doppler US, is required. The detection rate is nearly 100% [169-172]. However, it can be challenging to differentiate between benign and malign tumours through US alone. In adults, smaller tumour size, heterogenous masses, hyperechogenicity, peripheral Doppler flow and nonenhancement on US have a significantly lower OR of malignancy, however, evidence for prepubertal males is scarce [173].

Microlithiasis

With high-resolution US, microlithiasis (hyperechoic, non-shadowing foci 1-3mm in diameter within the testicular parenchyma) is increasingly seen in prepubertal boys. The incidence of microlithiasis is significantly higher in patients who had undergone orchiopexy [174]. Routine monthly self-examination of the testes is recommended in children with microlithiasis with contributing risk factors from puberty onwards [12]. When microlithiasis is still present during transition to adulthood, a more intensive follow-up could be considered. Due to the low incidence of a contralateral tumour, even in cases of testicular microlithiasis, there is no indication for contralateral testicular biopsy in prepubertal boys [173].

Tumour markers

When tumour markers are used, age of the patient should be taken into account, since alpha-fetoprotein (AFP) has a clear limitation of its sensitivity and specificity in the first months of life [167], and sometimes takes up to 12 months before the serum concentration reaches the known standard values (<ng/mL) [158, 175]. AFP is produced by >90% of yolk sac tumours. Teratomas can also produce AFP, but not to that extent of yolk sac tumours [176]. Alpha-fetoprotein should be measured before any therapeutic intervention (tumour enucleation/orchiectomy) and should be measured five days after tumour resection/orchiectomy in those with an elevated AFP according to the half-life time of AFP. Human chorionic gonadotropin (ß-hCG) is derived from chorion carcinoma, embryonal carcinoma or seminoma. However, these tumours are extremely rare in prepubertal boys and therefore ß-hCG is not a useful tumour marker in prepubertal boys.

Staging

In patients with a malignant tumour (yolk sac tumour, immature teratoma), staging should be performed, including either a CT scan or MRI of the abdomen and a CT scan of the chest. If there is any suspicion of a non-organ-confined tumour, the patient should be referred to a paediatric oncologist. In patients with the rare diagnosis of a Granulosa cell tumour, imaging of the abdomen to exclude enlarged lymph nodes is reasonable, as this may be a potentially malignant tumour. In those with Sertoli or a Leydig cell tumour, an MRI is recommended, because 10% are malignant and the metastases do not respond very well to chemotherapy or radiation in the adult literature [177, 178]. For information about staging of testicular tumours, we refer to the EAU Guidelines on Testicular Cancer [142]. In benign tumours (mature teratoma, epidermoid cysts), no further staging is required.

5.4 Treatment/management

If a testicular tumour is suspected, surgery with the option of intraoperative frozen section should be performed. It is not necessary to do this as an emergency procedure. However, to confirm the diagnosis and to avoid familial anxiety, the operation should be scheduled as soon as possible, preferably within the next few days. Whenever possible, testis-sparing surgery (TSS) should be performed. In a systematic review, the recurrence rate after surgery was found to be 5.8% (95% CI: 2.3-14.1%) in cohorts, including a benign rate of 70.9% [179]. Testis-sparing surgery was performed in 36.2% of these patients.

When performing TSS, frozen sections during surgery can be performed to confirm the diagnosis (benign vs. malignant tumour) and to confirm whether a microscopically margin-negative resection is performed, in which no gross or microscopic tumour remains in the primary tumour bed (R0 resection). In cases of an R0 resection, the tunica is closed and the testis is replaced in the scrotum. In case of R1 resection (removal of all macroscopic disease, but microscopic margins are positive for tumour) confirmed by frozen section in a malignant or potential malignant tumour, an orchiectomy should be performed at the same time of surgery. If the final pathology later demonstrates an R1 resection in a malignant tumour despite intraoperative negative margins on frozen section, an inguinal orchiectomy can be safely performed. Similarly, in a multicentre retrospective study, intraoperative biopsy followed by tumorectomy to preserve healthy testicular tissue in benign testicular tumours was recommended [180].

Orchiectomy could be considered only if normal testicular parenchyma is no longer detectable in the preoperatively high-resolution US and/or if the AFP is >100ng/mL in a >12-month-old boy, which is highly suspicious of a yolk sac tumour.

For surgical technique, the Panel is in favour of an inguinal approach. Moreover, clamping of the vessels has the advantage of offering a better view when organ sparing surgery is performed. However, there is no evidence in the literature that tumour-spread is prevented by clamping the vessels. In addition, a retrospective multicentre study suggested that a scrotal approach may be applied for selected cases [181].

As most paratesticular tumours are benign, intraoperative frozen section should be available during surgery and organ-sparing surgical approach is preferred in benign tumours. If a paratesticular rhabdomyosarcoma is suspected, radical inguinal orchiectomy should be performed if tumour size allows it. Otherwise, it is better to extend the inguinal incision down to the scrotum or use a combined inguinal and scrotal approach to facilitate a complete gross total tumour resection [182].

5.5 Tumour entities in prepubertal boys

*5.5.1 **Germ cell tumours***

Teratomas are usually benign in prepubertal children and represent the greatest proportion of intratesticular tumours (approximately 40%) [153, 183]. Teratomas present at a median age of 13 months (0-18 months).They should only be considered malignant tumours in adolescents and adults. Histologically, they can consist of a combination of the three primitive embryological germ-cell layers (ectoderm, mesoderm and endoderm). Most of these elements show microscopically mature elements [184], however, some immature teratomas in this age group have also been reported [185]. Upon US examination, a heterogenous picture with some calcification is seen [186] and AFP should be less than 100ng/mL in an infant. After organ-sparing surgery, only one recurrence was reported in the literature [187].

Epidermoid cysts are of ectodermal origin and seem to be related to well-differentiated teratomas. They are always benign [184]. Keratin-producing epithelium is responsible for the keratinised-squamous-epithelial deposits, which appear hyperechogenic in a US [186]. Organ-sparing surgery should be performed and, if confirmed by histology, there is no need for surveillance despite the fact that one 'recurrence' has been reported thirteen years after diagnosis [188].

Yolk sac tumours are the predominant prepubertal malignant germ cell tumours and represent approximately 15% of the prepubertal tumours in boys [153]. Yolk sac tumours usually occur within the first two years of life [189]. Histologically, they are mostly solid, yellow-grey tumours, and up to 80-85% of the tumours are organ-confined (Stage I) [190]. Yolk sac tumours are associated with elevated AFP levels, which is seen in more than 90% of cases [191]. The tumour usually spreads haematogenously, and 20 percent of those presenting initially with Stage I disease (no metastatic disease in the MRI-abdomen and CT scan of the chest, as well as normal age-adapted AFP values) may develop visible metastases within the next two years. Therefore, close follow-up together with the paediatric oncologists including AFP every two to three months and MRI of the abdomen is recommended, at least for the first two to three years [167]. This is especially recommended in those patients with invasions of the lymphatic vessels, because this has been shown to be a prognostic factor [189]. In cases of recurrence, chemotherapy should be performed by paediatric oncologists according to national study protocols [192]. The overall three-year and five-year survival rates of patients with a yolk sac tumour were 96.1% and 95.3%, respectively [193].

*5.5.2 **Gonadal stromal tumours***

Juvenile granulosa cell tumours typically occur within the first six months of life They are well circumscribed and have a typical yellow-tan appearance; two-thirds have cystic elements and one-third are solid. A systematic review in which all case series were pooled showed that in all 166 patients described the disease was benign [194].

Sertoli cell tumours usually occur within the first year of life [195]. In the paediatric age group, the large-cell calcifying Sertoli cell tumours (LCCSCT) is the most common tumour variant [196, 197]. They can occur in patients with complex dysplastic syndromes, such as the Carney or Peutz-Jeghers syndrome [197-199]. With the exception of one case report with the histological diagnosis of a malignant LCCSCT [196], all other reported tumours are benign. Therefore, organ-sparing surgery should be performed.

Leydig cell tumours arising from the testosterone producing Leydig cells should be suspected in boys with early onset of puberty with high testosterone and low gonadotropin levels [168]. Patients are usually between six and ten years of age, and the tumours are well-circumscribed with yellow-brown nodules. There are no reports of malignant Leydig cell tumours in children, and after organ-sparing surgery, there are no reported recurrences [200, 201]. The adult literature reports a malignancy rate of 10%, and primary retroperitoneal lymphadenectomy should be discussed in cases with enlarged lymph nodes, because these metastases do not respond very well to chemotherapy or radiation [202].

*5.5.3 **Other tumours***

Testicular adrenal rest tumours (TARTs) can occur in boys with a congenital adrenal hyperplasia (CAH). Up to one-third of the TARTs occurs prepubertally, and the proportion increases with age. A significant correlation exists with poor hormonal control [203-205]. In a comparative study, factors found to correlate with TARTs volume included ACTH levels (coefficient 0.004; $p = 0.009$) and the three-year average of serum testosterone levels (coefficient 9.64; $p = 0.003$) [206]. A delayed CAH diagnosis of over one year was associated with a 2.6x higher risk of TART [207]. While TARTs have no malignant potential, they can have a lasting impact on fertility by displacing the normal testicular parenchyma [208, 209]. These patients should be offered US screening and advice on fertility with the option of cryopreservation [209]. A cross-sectional clinical study found that the size of the TART affects the volume of residual spermatogenic testicular tissue, while current CAH control impacts adrenal androgen hypersecretion [210].

5.6 Follow-up

Regular US examination is recommended in the follow-up period to detect any recurrence and/or other abnormalities. As there are only a few studies with recurrence after testicular-sparing surgery or orchiectomy, no clear recommendation can be made concerning the interval and the duration of follow-up. However, performing a US examination every three to six months within the first year seems reasonable, because few recurrences have been detected at this time and the rate of atrophy is extremely low after organ-sparing surgery [211]. Only in patients with a malignant tumour, regular follow-up examination after the first year of surgery seems reasonable (see above). The follow-up in patients with a Leydig cell tumour should include endocrinological examinations.

Summary of evidence	LE
Testicular tumours in prepubertal boys are rare and have a different histologic distribution compared to the adolescent and adult patients.	2a
Up to 60-75% of testicular tumours in prepubertal boys are benign.	3

Recommendations	Strength rating
High-resolution ultrasound (7.5-12.5MHz), preferably a doppler ultrasound, should be performed to confirm the diagnosis.	Strong
Alpha-fetoprotein should be determined in prepubertal boys with a testicular tumour before surgery.	Strong
Surgical exploration should be performed with the option for frozen section.	Strong
Testicular sparing surgery should be performed in all benign tumours.	Strong
Staging (MRI abdomen/CT chest) should only be performed in patients with a malignant tumour to exclude metastases.	Strong
Patients with a non-organ-confined tumour should be treated in a multidisciplinary fashion, including paediatric oncologists.	Strong

6. FERTILITY PRESERVATION IN CHILDREN AND ADOLESCENTS

The continuous increase in the incidence of paediatric cancers and post-treatment survivorship over the years, coupled with the further development of potentially gonadotoxic therapies, has contributed to the recognition and rapid endorsement of fertility-preservation counselling for prepubertal children and adolescents. Patients and caregivers should be informed not only about the impact of gonadotoxic treatments on future fertility, but also about fertility-preservation options and their risk-benefit ratio. There are also several nononcological congenital anomalies where fertility preservation can become an issue.

This chapter focuses on basic information on cryopreservation indications and options for paediatric urologists. For more detailed information, we refer to specific guidelines on this topic [212-214].

6.1 Ovarian tissue cryopreservation in prepubertal and adolescent girls

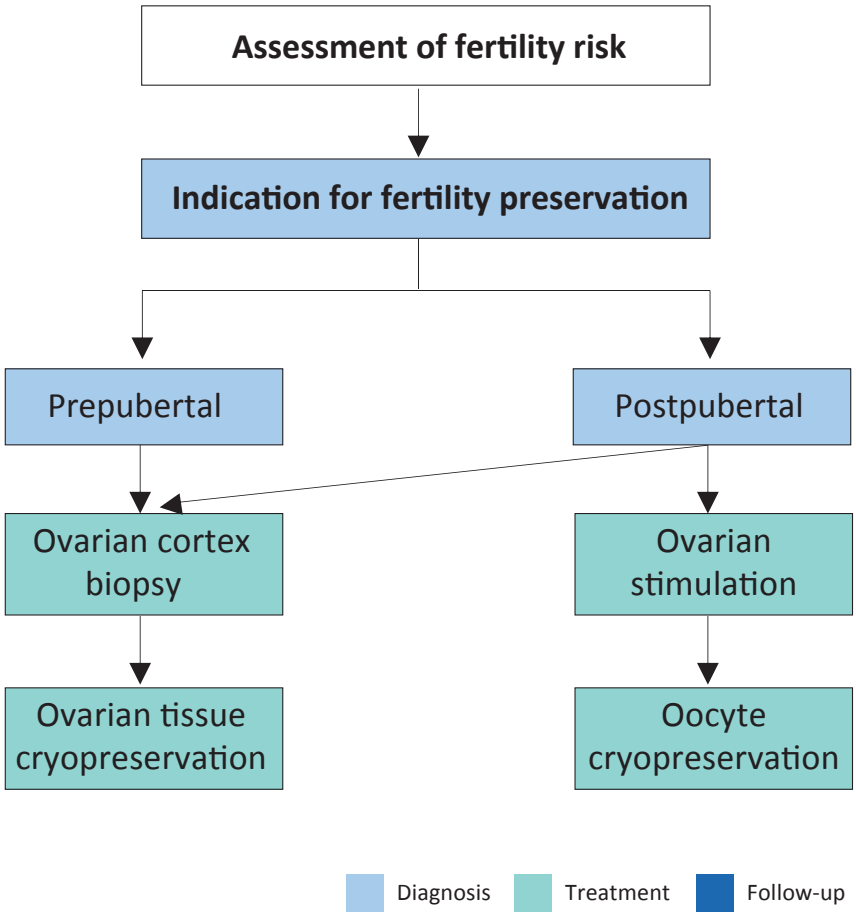
Infertility in the paediatric and adolescent population can result from direct gonadal damage from surgery, or gonadal toxicity as a result of chemotherapy or radiation [212]. Frequent indications requiring gonadotoxic therapy include solid tumours, leukaemia and benign indications, such as hemoglobinopathies [215]. First-line chemotherapy does not appear to affect the number of primordial follicles [216]. Rather, it seems to have a significant effect on the health, density and functionality of follicles [217], resulting in a reduction of 10-30% of ovarian reserve, depending on age and menarchal status [218]. The indication and options for fertility preservation should ideally be discussed in a paediatric multidisciplinary fertility preservation team and should consider the toxicity of the planned therapy, the age and menarchal status, as well as ethical and financial issues [219, 220].

In paediatric and adolescent patients, ovarian tissue retrieval is performed by removal of an entire ovary (or partial ovariectomy) by laparoscopy [221], or in the setting of a laparotomy for surgery of the primary tumour [215, 222]. It is advised to combine these interventions with other medically indicated procedures to minimise any additional anaesthetic risks and costs [223]. In postpubertal patients and in the setting of benign disease, oocyte retrieval following prior ovarian stimulation can be performed [224-227]. For patients undergoing brachytherapy of the pelvic region, the technique of temporary laparoscopic ovarian transposition has been described [228].

Ovarian tissue can be reimplanted orthotopically or heterotopically. For fertility purposes, orthotopic transplantation includes implanting ovarian tissue into the peritoneal cavity, the remaining contralateral ovary, the ovarian fossa or the broad peritoneal ligament [229]. Heterotopic transplantation includes transplantation

of ovarian tissue into other locations, such as the subcutaneous abdominal wall, the rectus muscle and the forearm. This technique can be used for the recovery of natural endocrine function [229]. The utilisation rate of ovarian tissue for ovarian cortex autotransplantation in the paediatric population has been reported to be as low as 2.2-5% [226, 230, 231]. A large case series demonstrated that transplantation of prepubertal cryopreserved ovarian tissue resulted in induction of spontaneous puberty and pregnancies in a few reported cases. However, only a few cases with long-term outcomes are reported in the literature [232, 233].

Figure 3: Ovarian tissue cryopreservation for girls and adolescents



Adapted from Anderson et al., [227].

6.2 Cryopreservation in prepubertal and adolescent boys

The increase in the incidence of paediatric cancers and post-treatment survivors has also contributed to studies for fertility preservation in prepubertal boys. Gonadoprotective measures aiming at protecting the survival and function of immature germ cells in prepubertal testes, which are highly susceptible to irradiation and chemotherapy, should be the first aim [234]. Attenuation of externally scattered irradiation from fields close to the testes by gonadal shielding has been shown to be effective with respect to testicular growth in survivors [235, 236]. In patients undergoing brachytherapy in the genital region, temporary testicular transposition has been described as a method for fertility preservation [237].

Sperm cryopreservation via masturbation or penile vibration should be the first option in nonazoospermic postpubertal boys. Techniques such as electroejaculation should only be discussed in very specific circumstances. Cryopreservation of immature testicular tissue, containing spermatogonial stem cells, as a fertility preservation option for this population is still experimental and should be carefully explained to caregivers and patients by a multidisciplinary team [234]. Testicular biopsy procedures do not seem to affect fertility potential, due to surgical complications or due to disruption of the blood-testicular barrier. However, further studies on this topic are needed [238].

Additional anaesthesia-related risks for testicular sampling should be avoided, if possible. The procedure can be combined with any other intervention requiring anaesthesia whenever possible [234].

For benign conditions such as Klinefelter Syndrome, with the potential risk of germ cell loss prior to puberty, bilateral undescended testes cryopreservation has been proposed but remains controversial and experimental [239-241].

Even though experimental advances have been achieved in non-human primates, many challenges remain to be addressed for prepubertal testes before clinical application.

6.3 Summary of evidence and recommendations fertility preservation in children and adolescents

Summary of evidence
It is advised to combine any fertility preservation intervention with other medically indicated procedures to minimise additional anaesthetic risks and costs
Ovarian tissue cryopreservation can be used for fertility preservation in pre- and postpubertal girls.
Cryopreservation of immature testicular tissue, containing spermatogonial stem cells, as a fertility preservation option for this population is still experimental and should be well explained to caregivers and patients by a multidisciplinary team.

Recommendations	Strength rating
Inform patients and caregivers about the impact of gonadotoxic treatments on future fertility and about fertility preservation options and their risk-benefit balance.	Strong
Discuss the indications and options for fertility preservation in a paediatric multidisciplinary fertility preservation team and consider the toxicity of the planned therapy, the age and pubertal status as well ethical and financial issues.	Strong

7. HYDROCELE

7.1 Epidemiology, aetiology and pathophysiology

Hydrocele is defined as a collection of fluid between the parietal and visceral layers of the tunica vaginalis [242]. In males, congenital hydrocele is based on failed obliteration of the processus vaginalis between the inguinal canal and scrotum. Similarly, although rarer, hydrocele can occur in females with failed obliteration of the canal of Nuck - a protrusion of peritoneum in the female inguinal canal. There are various types of congenital hydrocele. In communicating hydrocele, intraperitoneal fluid passes into the scrotal tunica vaginalis due to persisting patency of the processus vaginalis (PPV). This must be differentiated from inguinal hernia, in which the processus vaginalis is wide enough to allow passage of abdominal viscera or omentum [242]. If obliteration of the processus vaginalis occurs with focal patency of the mid-portion, a hydrocele of the cord occurs. The exact time of spontaneous closure of the inguinal processus vaginalis is not known. Processus vaginalis is present in approximately 80-94% of newborns and in 20% of adults [243]. Scrotal hydroceles without associated patency of the inguinal processus vaginalis may be encountered in newborns [244]. However, such noncommunicating hydroceles are often acquired and based on an imbalance between the secretion and reabsorption of lymphatic fluid, and thus can be found secondary to minor trauma, testicular torsion, epididymitis, varicocele operation (due to ligation of the lymphatics) or may appear as a recurrence after hydrocele repair. In rare cases, a hydrocele may have an intra-abdominal component, positioned ventral or dorsal to the bladder: the so-called abdominoscrotal hydrocele (ASH). This is considered a scrotal hydrocele with an hourglass-shaped extension reaching into the abdomen via the inguinal ring. Abdominoscrotal hydrocele may be associated with testicular dysmorphism related to increased pressure [245, 246].

7.2 Diagnostic evaluation

The classic description of a communicating hydrocele is that of a hydrocele that fluctuates in size and is usually related to ambulation. Communicating hydrocele may be diagnosed through history-taking and physical investigation. The presence of contralateral disease should be addressed during the initial consultation [243]. Transillumination of the scrotum provides the diagnosis in the majority of cases, bearing in mind that fluid-filled intestine and some prepubertal tumours may transilluminate as well [247, 248]. In hydroceles, the swelling is smooth and usually not tender. If there are any doubts about the character of an intrascrotal mass or if the testis is not palpable, scrotal US, which has nearly 100% sensitivity in detecting intrascrotal lesions, should be considered. Doppler US studies help to distinguish hydroceles from varicocele and testicular torsion, although

these conditions may also be accompanied by a hydrocele [249]. Presence of ASH is suggested by a tense hydrocele or palpable abdominal extension upon compression of the scrotal part of the hydrocele and can be confirmed by US [246].

7.3 Management

Conservative management

In the majority of infants, observation is warranted at least within the first twelve months due to the tendency of spontaneous resolution [250]. The rate of resolution decreases with age, with 92% resolution below one year old and 43% above three years [251, 252]. Initial observation poses little risk, as progression to hernia is rare and does not result in incarceration [250]. There is no evidence that hydrocele risks testicular damage [252]. In acquired hydrocele suggestive of a non-communicating hydrocele, there is still a reasonable chance of spontaneous resolution (75%), and expectant management of six to nine months is recommended [253]. In ASH, the rate of spontaneous resolution appears lower, although it has been reported [254]. In exemption to the above, the suspicion of a concomitant inguinal hernia or underlying testicular pathology necessitates early surgery [255]. In other cases, initial conservative treatment may reduce the number of procedures without increasing morbidity, however, persistence of hydrocele is an indication for surgical correction.

Surgical treatment

In the paediatric age group, surgical correction consists of inguinal ligation of the patent processus vaginalis via inguinal incision with the distal stump being left open. In hydrocele of the cord, the cystic mass is excised or unroofed [248, 256, 257]. In expert hands, the incidence of testicular damage during hydrocele or inguinal hernia repair is very low. Laparoscopic hernia repair with percutaneous ligation of the patent inguinal processus vaginalis is a minimally invasive alternative to open inguinal herniorrhaphy [258, 259]. In line with these techniques, various laparoscopic techniques for hydrocele correction have been described. No technique appears to be superior [243].

Laparoscopic correction of a contralateral patent processus may be considered, however, a recent meta-analysis found insufficient evidence to recommend this for inguinal hernia [243] and hydrocele was not reported. The incidence of patent contralateral processus appears much higher than the percentage of children developing metachronous hernia (63% vs 8%) [243]. Thus, to prevent metachronous inguinal hernia, the number needed to treat is relatively high (NNT = 18) [260]. For acquired, noncommunicating hydrocele, the scrotal approach (Lord or Jaboulay/Winkelmann technique) is used.

In ASH, most case series describe resection of the abdominal component, which is connected to the scrotal, but not to the inguinal processus vaginalis. The incidence of complications for this procedure is higher than in regular hydrocele repair [254] and can result in testicular loss and atrophy, causing some to question if resection is necessary [246, 254]. Larger series are needed to assess optimal management. Testicular dysmorphism may recover following surgery [245]. Sclerosing agents should not be used due to the risk of chemical peritonitis in communicating processus vaginalis [248].

7.4 Summary of evidence and recommendations for the management of hydrocele

Summary of evidence
In the majority of infants, surgical treatment of hydrocele is not indicated within the first twelve months due to the tendency for spontaneous resolution. Little risk is taken by initial observation as progression to hernia is rare.
In acquired hydrocele, initial expectant is recommended, unless hernia or testicular pathology are suspected.
In the paediatric age group, an operation would generally involve ligation of the patent processus vaginalis via inguinal incision.

Recommendations	Strength rating
Observe hydroceles in the majority of infants prior to considering surgical treatment.	Strong
Perform early surgery if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology.	Strong
Perform ultrasound in case of doubt about the character of an intrascrotal mass, or suspicion of an abdominoscrotal hydrocele.	Strong
Close the processus vaginalis at the inguinal ring.	Strong

Do not use sclerosing agents in children with hydroceles, because of the risk for chemical peritonitis.	Strong

8. ACUTE SCROTUM

8.1 Epidemiology, aetiology and pathophysiology

Acute scrotum is a paediatric urological emergency, most commonly caused by torsion of the testis or appendix testis, or epididymitis/epididymo-orchitis [261-266]. Other causes of acute scrotal pain are idiopathic scrotal oedema, mumps orchitis, varicocele, scrotal haematoma, incarcerated hernia, appendicitis or systemic disease (e.g. Henoch-Schönlein purpura) [267-279]. Trauma can also be a cause of acute scrotum, as it can relate to post-traumatic haematomas, testicular contusion, rupture dislocation or torsion [280-285]. Scrotal fat necrosis has also been reported to be an uncommon cause of mild-to-moderate scrotal pain in prepubertal overweight boys after exposure to cold [286].

This chapter discusses testicular torsion and epididymitis, while recurrent epididymitis is discussed in the chapter dealing with infections. Torsion of the testis occurs most often in the neonatal period and around puberty, whereas torsion of the appendix testis occurs over a wider age range.

Epididymitis affects two age groups: less than one year and twelve to fifteen years [287, 288]. One study predicted the annual incidence of epididymitis at around 1.2 per 1,000 children [289]. Perinatal torsion of the testis (PTT) most often occurs prenatally. Bilateral torsion comprises 11-21% of all perinatal cases [290, 291]. Most cases are extravaginal, in contrast to the usual intravaginal torsion, which occurs during puberty.

8.2 Diagnostic evaluation

Patients usually present with scrotal pain, except in neonatal torsion. The sudden onset of severe pain in combination with a vagal reaction (e.g. nausea, vomiting) is typical for torsion of the testis or appendix testis [292, 293]. As the probability of irreversible changes and subsequent necrosis in testicular torsion is time-dependent with a critical window of approximately four to six hours, prompt diagnosis is essential [294].

In general, the duration of symptoms is shorter in testicular torsion (69% present within twelve hours) and torsion of the appendix testis (62%) compared to epididymitis (31%) [263, 264, 288].

In the early phase, location of the pain can lead to diagnosis. Patients with acute epididymitis experience a tender epididymis, whereas 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 [288].

An abnormal (horizontal) position of the testis is more frequent in testicular torsion than epididymitis [263]. Looking for absence of the cremasteric reflex is a simple method with 100% sensitivity and 66% specificity for testicular torsion [287, 293]. Elevation of the scrotum may reduce complaints in epididymitis, but not in testicular torsion (Prehn Sign). Testicular torsion can also occur in undescended testes [295].

Fever occurs more often in epididymitis (11-19%). The classical sign of a 'blue dot' was found only in 10-23% of patients with torsion of the appendix testis [262, 263, 287, 296]. In many cases, it is not easy to determine the cause of acute scrotum based on history and physical examination alone [261-266, 287, 296]. A positive urine culture is only found in a few patients with epididymitis [265, 287, 296, 297]. It should be remembered that a normal urinalysis does not exclude epididymitis. Similarly, an abnormal urinalysis does not exclude testicular torsion.

The urological history and clinical findings can be used for risk-scoring to expedite the diagnostic process to identify testicular torsion as exemplified by the Testicular Workup for Ischemia and Suspected Torsion (TWIST) [298]. While risk-scoring systems such as TWIST may assist in streamlining decision-making, they do not conclusively prove or refute the diagnosis of testicular torsion and should not be solely relied upon. Incorporating scoring systems into the assessment can help reduce potential delays, although current evidence does not provide definite support from a medicolegal standpoint for conclusive decision-making [299-301]. Nevertheless, it may be prudent to consider lowering thresholds for intervention within the scoring systems in settings with limited diagnostic facilities.

Doppler US is useful to evaluate acute scrotum, with 63.6-100% sensitivity and 97-100% specificity, a positive predictive value of 100% and negative predictive value of 97.5% [302-307]. The use of Doppler US 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 [304, 308]. It may also show a misleading arterial flow in the early phases of torsion and in partial or intermittent torsion. Of key importance, persistent arterial flow does not exclude testicular torsion. In a multicentre study of 208 boys with torsion of the testis, 24% had normal or increased testicular vascularisation [304]. A comparison with the other side should always be done. Point-of-care US (POCUS) in emergency settings performed by the treating physician shows high sensitivity and specificity for testicular torsion in a systematic review, however, a risk of bias persists in the baseline studies [309]. Nevertheless, POCUS can aid in streamlining the diagnostic process.

Better results were reported using high-resolution US (HRUS) for direct visualisation of the spermatic cord twist with a sensitivity of 97.3% and specificity of 99% [304, 310]. This should be done without inordinate delays for emergency intervention [296].

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 US might suggest an erroneous diagnosis of epididymitis in children with torsion of the appendix testes [311]. Prepubertal boys with acute epididymitis have an incidence of underlying urogenital anomalies of 29.1% [312]. Complete urological evaluation in all children with acute epididymitis is still debatable [265, 287, 289].

8.3 Management

*8.3.1 **Epididymitis***

In prepubertal boys, the aetiology is usually unclear, with an underlying pathology in 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 [289, 313, 314]. Epididymitis is usually self-limiting and with supportive therapy (i.e. minimal physical activity and analgesics) heals without any sequelae. However, bacterial epididymitis can be complicated by abscess or necrotic testis, in which case surgical exploration might be required [315].

*8.3.2 **Testicular torsion***

Surgical exploration is necessary in the setting of testicular torsion. If testicular torsion is confirmed, contralateral orchiopexy is commonly performed as well [316]. 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 [317, 318]. Manual detorsion of the testis can be attempted in the ER while awaiting surgery and should not delay surgery [319]. Manual detorsion should be done using outward 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 [317]. Doppler US may be used for guidance [320].

Torsion of the appendix testis can be managed nonoperatively with the use of anti-inflammatory analgesics. During the six-week follow-up, clinically and with US, no testicular atrophy was revealed. Surgical exploration is done in equivocal cases and in patients with persistent pain [307].

*8.3.3 **Surgical treatment***

Testicular torsion is an urgent condition that requires prompt surgical treatment. The two most important determinants of early salvage rate of the testis are the time between onset of symptoms and detorsion, and the degree of cord twisting [294]. Severe testicular atrophy occurred after torsion for as little as four hours when the turn was >360°. In cases of incomplete torsion (180-360°) 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 >360° and symptom duration >24 hours [321].

Early surgical intervention with detorsion (mean torsion time less than 13 hours) was found to preserve fertility [322] and could also avoid testicle loss in a relevant portion of patients [295]. Urgent surgical exploration is mandatory in all cases of testicular torsion within 24 hours of symptom onset. In patients with testicular torsion >24 hours, semielective exploration is necessary [294, 321]. There is still controversy regarding whether to carry out detorsion and to preserve the ipsilateral testis, or to perform an orchiectomy, to preserve contralateral function and fertility after testicular torsion of long duration (>24 hours). A study found that sperm quality was

preserved after orchiectomy and orchidopexy in comparison to normal control men, although orchiectomy resulted in better sperm morphology [323, 324]. However, larger testicular volumes have been associated with enhanced testicular function, suggesting a conservative approach to preserving the affected testicle unless it is unequivocally necrotic [325]. Although Sertoli cell function depends primarily on the contralateral testis, the torsed testicle may contribute to endocrine function.

Recurrence after orchidopexy is rare (4.5%) and may occur several years later. There is no consensus recommendation regarding the preferred type of fixation and suture material [316, 326]. Incision of the tunica albuginea with tunica vaginalis graft to prevent or treat compartment syndrome has also been suggested [327], however, immediate effect on intratesticular pressure is vague with unclear long-term benefits [328].

Metachronous contralateral torsion may occur in perinatal testicular torsion. Therefore, early but not acute exploration of both testes with fixation is recommended [290, 291, 329].

8.4 Follow-up

Patients require follow-up mainly for fertility issues and hormonal consequences. Despite timely and adequate detorsion and fixation of the testicle, up to half of the patients may develop testicular atrophy, even when intraoperatively assessed as viable, and should be counselled accordingly [330].

*8.4.1 **Fertility***

The results vary and are conflicting. In one study, unilateral torsion of the testis seriously intervened with subsequent spermatogenesis in approximately 50% of the patients and produced borderline impairment in another 20% [331]. Although, 30% of affected testicles with mumps orchitis show a degree of atrophy, long-term outcome in terms of fertility is not conclusive [332].

A study showed a normal pregnancy rate after unilateral testicular torsion, with no difference between the patients undergoing orchidopexy and those after orchidectomy [329].

*8.4.2 **Subfertility***

Subfertility is found in 36-39% of patients after torsion. However, in a limited series, paternity and health-related quality of life (QoL) appear to be unaffected in patients as compared to age-matched controls in a long-term follow-up study [334]. Semen analysis may be normal in only 5-50% in long-term follow-up [294]. Early surgical intervention (mean torsion time less than 13 hours) with detorsion was found to preserve fertility, but prolonged torsion period (mean 70 hours) followed by orchiectomy jeopardised fertility [322].

Subfertility and infertility are consequences of direct injury to the testis after the torsion. This is caused by the cut-off of blood supply, but also by postischaemic-reperfusion injury that is caused after the detorsion when oxygen-derived free radicals are rapidly circulated within the testicular parenchyma [294].

*8.4.3 **Androgen levels***

Even though the levels of FSH, luteinising hormone (LH) and testosterone are higher in patients after testicular torsion compared to normal controls, endocrine testicular function remains in the normal range after testicular torsion [323, 325].

Summary of evidence	**LE**
Diagnosis of testicular torsion is based on presentation and physical examination.	3
Doppler US is an effective adjunctive imaging tool to evaluate acute scrotum.	2a
The earlier surgical intervention for testicular torsion is performed, the better the outcome for testicular histology. Ideally within 4-6 hours after the onset of symptoms.	3
Metachronous contralateral torsion can occur in perinatal torsion, warranting early, but not acute exploration.	3

Recommendations	**Strength rating**
Testicular torsion is a paediatric urological emergency and requires immediate treatment.	Strong
In neonates with testicular torsion perform orchidopexy of the contralateral testicle. In prenatal torsion, the timing of surgery is usually dictated by clinical findings.	Weak

Base the clinical diagnosis on physical examination. The use of Doppler US to evaluate acute scrotum is useful, but this should not delay the intervention.	Strong
Manage torsion of the appendix testis conservatively. Perform surgical exploration in equivocal cases and in patients with persistent pain.	Strong
Perform urgent surgical exploration in all cases of testicular torsion as soon as possible.	Strong

9. HYPOSPADIAS

9.1 Epidemiology, aetiology, and pathophysiology

*9.1.1 **Epidemiology***

The total prevalence of hypospadias in Europe is 18.6 new cases per 10,000 male births (5.1-36.8) according to the EUROCAT registry-based study [335]. Worldwide, there is variation in the prevalence of hypospadias according to an extended systematic literature review: Europe 19.9 (range: 1-464), North America 34.2 (6-129.8), South America 5.2 (2.8-110), Asia 0.6-69, Africa 5.9 (1.9-110), and Australia 17.1-34.8 per 10,000 [336].

9.2 Risk factors

Risk factors associated with hypospadias are likely to be genetic, placental and/or environmental [337-339]. Interactions between genetic and environmental factors (endocrine-disrupting chemicals) may help explain nonreplication in genetic studies of hypospadias [340, 341].

The following risks factors has been associated with hypospadias:

- An additional family member with hypospadias is found in 7%-12.9% of families and is more predominant in anterior and middle forms [342, 343].
- Infants with low birth weight or being small for gestational age (SGA) have a higher risk of hypospadias [342]. Furthermore, SGA might also be associated with a higher reoperation rate in proximal hypospadias [337, 343, 344].
- Maternal hypertension during pregnancy and preeclampsia has been shown to be associated with hypospadias, likely due to that both factors may be associated with placental dysfunction [337].
- Pregestational diabetes mellitus and gestational diabetes mellitus are associated with an increased risk of hypospadias in offspring [345].

9.3 Classification systems

Hypospadias is usually classified based on the anatomical location of the proximally displaced urethral orifice [346]:

- distal-anterior hypospadias (located on the glans or distal shaft of the penis);
- intermediate-middle (penile); and
- proximal-posterior (penoscrotal, scrotal, perineal).

The pathology may be different after skin release and should be reclassified accordingly [347]. The anatomical location of the meatus may not always be enough to explain the severity and the complex nature of this pathology. When evaluating the severity of the hypospadias, the consensus of the Panel is to consider factors such as penile length, penile curvature, glans size and shape, and urethral plate quality.

9.4 Diagnostic evaluation

Most hypospadias patients are easily diagnosed at birth (except for the megameatus intact prepuce variant, which can only be seen after retraction of foreskin). Diagnosis includes a description of the local findings:

- position, shape and width of the meatal orifice;
- presence of atretic urethra and division of corpus spongiosum;
- appearance of the preputial hood and scrotum;
- size of the penis; and
- curvature of the penis on erection.

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

- congenital cryptorchidism (2%-6.2%) [348, 349]
- acquired undescended testes (1%-14%) [348-350]

In hypospadias patients with bilaterally undescended testis, complete genetic and endocrine workup soon after birth to exclude DSD, particularly congenital adrenal hyperplasia [66]. Urine trickling and ballooning of the urethra requires exclusion of meatal stenosis. There are conflicting data on presence of additional birth defects in urogenital system (e.g. UPJ stenosis, renal agenesis and dysgenesis, cystic kidney disease) in hypospadias patients with unrecognised syndromes. The Panel consensus it not to perform imaging studies in hypospadias patients.

9.5 Management

The natural history of untreated hypospadias is poorly documented. Studies of adult men with uncorrected, mainly distal, hypospadias have shown conflicting results. Early reports indicate normal voiding, sexual function and high satisfaction with penile appearance, despite an abnormal position of the urethral meatus [351, 352]. More recent studies have reported urinary spraying, urinary obstruction, penile curvature, coital pain and dissatisfaction with genital appearance in adult men with untreated hypospadias [353-355]. Notably, more than half of these men opted for surgical correction [353, 354].

*9.5.1 **Indication for reconstruction and therapeutic objectives***

Therapeutic decision-making regarding hypospadias surgery includes distinguishing between functionally essential and aesthetically feasible procedures. Aspects to be considered are voiding, sexual/reproductive function and cosmetic appearance.

Indications for surgery may be:

- proximally located (ectopic) meatus causing ventrally deflected or spraying urinary stream;
- meatal stenosis;
- ventral curvature of the penis;
- preputial hood; and
- penoscrotal transposition.

As all surgical procedures carry the risk of complications, thorough preoperative counselling of the caregiver is crucial to reduce the chance of decisional regret.

To achieve an overall acceptable functional and cosmetic outcome, the penile curvature must be corrected with an adequate size neourethra. The meatus should be glandular, and the penile shaft should have proper skin coverage [356]. The use of magnifying loupes and fine synthetic absorbable suture materials (6.0-7.0) are required. As in any penile surgery, exceptional prudence should be adopted with the use of cautery. Bipolar cautery is recommended. Knowledge of a variety of surgical reconstructive techniques, wound care and postoperative treatment is essential for a satisfactory outcome.

*9.5.2 **Preoperative hormonal treatment***

There is inconclusive evidence to support the benefits of preoperative hormone therapy. The treatment is usually limited to patients with proximal hypospadias, a small-appearing penis, reduced glans circumference or narrow urethral plate [357-362].

There are concerns regarding the negative impact of testosterone on wound-healing and increased bleeding during surgery. Cessation of therapy is recommended one or two months prior to surgery to avoid adverse effects during or after surgery [363].

*9.5.3 **Age at surgery***

The age at surgery for primary hypospadias repair is usually 6-18 months [356, 364, 365]. Age at surgery is not a risk factor for urethroplasty complications in prepubertal tubularised incised plate urethroplasty (TIP) repair [364]. Complication rate after primary TIP repair was 2.5 times higher in adults than in the paediatric group, according to a prospective controlled study [366].

*9.5.4 **Penile curvature***

Some degree of penile curvature is common in hypospadias, and its severity is related to the severity of urethral abnormality. An erection test performed during hypospadias repair allows assessment of the degree of curvature. The use of measurement tools such as a goniometer or apps appears to improve accuracy compared to eyeballing assessment [367]. What degree of curvature is found to be clinically significant may differ between patients. Overall, curvature of 30 degrees or more is deemed to warrant correction [368].

For ventral curvature correction, a stepwise approach is recommended. The first step is degloving the penis (skin chordee) and excising abnormal connective tissue (chordee) on the ventral side of the penis [369].

In distal hypospadias, the urethral plate rarely causes curvature, as it has well characterised connective tissue [370, 371]. In severe hypospadias, curvature may be due to hinging of the urethral plate, which requires transection prior to ventral lengthening or dorsal plication. Urethral plate without transection is not recommended due to the risk of ventral curvature recurrence (20%) and stricture formation (17%) [368].

Residual curvature is believed to be caused by corporeal disproportion and requires adaptation of the corpora to enable straightening of the penis. This can be achieved using various techniques based on either dorsal shortening or ventral lengthening. Dorsoplication with or without excision of tunica albuginea (Nesbit plication) can be performed with or without elevation of the neurovascular bundle. The drawback of all dorsoplication techniques is shortening of the penis and potentially decreased sensitivity [372]. Penile length is one of the main reasons for dissatisfaction following hypospadias repair [368]. Ventral lengthening by various corporotomy techniques, with or without covering the defect, is safe and does not have these unwanted side-effects [373].

Several studies have suggested that, in cases of severe curvature ventral, lengthening may be superior to dorsoplication [372, 373]. The incidence of curvature-recurrence is less common with ventral lengthening than with dorsoplication (5% vs. 25%) [373], regardless of the technique used. Common procedures include multiple transverse corporotomies (such as fairy cuts or three corporotomies) or a single, wider corporoplasty. This is often covered by tunica vaginalis, although other tissues may have more contractions or are still under investigation [373]. Novel techniques using taping or stretching require further studies [374].

Risk factors for recurrence of ventral curvature are also related to the technique of urethral reconstruction. It has been shown that TIP for proximal hypospadias has a high recurrence rate of ventral curvature (26%). Conversely, the chosen method for penile straightening may impact the choice of urethral reconstruction. There is increasing evidence that corporoplasty with graft covering should not be performed simultaneously with urethral graft reconstruction [368].

9.5.5 ***Urethral reconstruction***

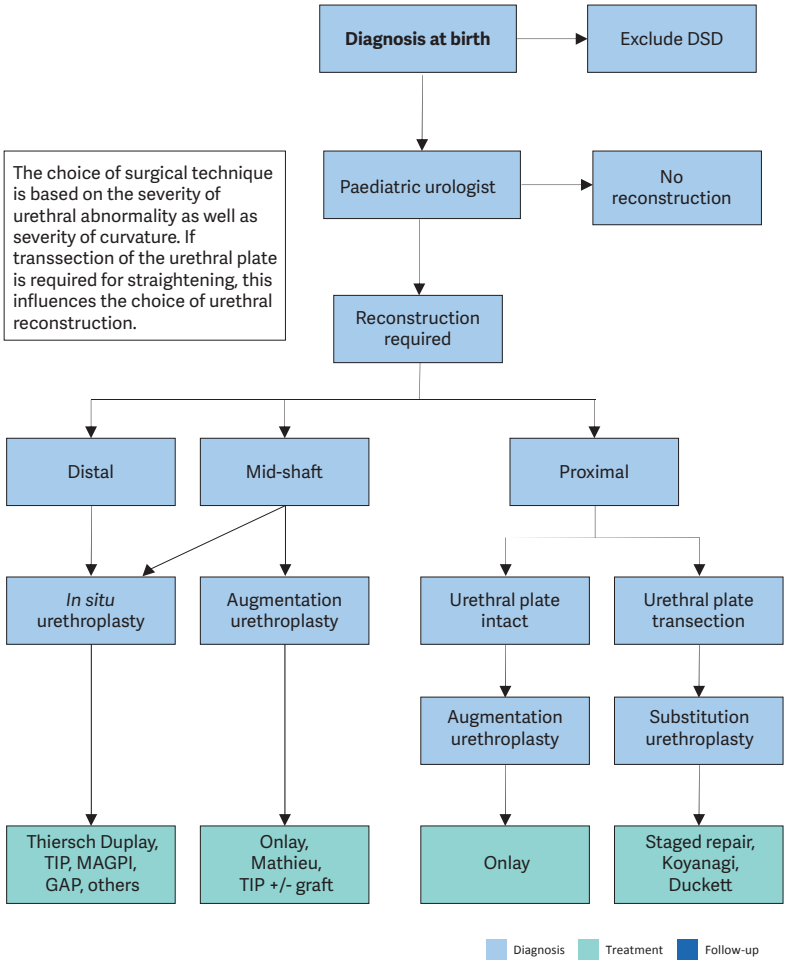
The mainstay of hypospadias repair is preservation of the well-vascularised urethral plate and its use for urethral reconstruction has become standard practice in hypospadias repair [371]. Mobilisation of the corpus spongiosum/urethral plate and the bulbar urethra decreases the need for urethral plate transection [375]. The use of a penile tourniquet during hypospadias repair can reduce operative time and improves intraoperative hemostasis without affecting postoperative outcomes [376].

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, a midline incision may facilitate subsequent tubularisation according to the TIP technique described by Snodgrass-Orkiszewski. This technique has become the treatment of choice in distal and mid-penile hypospadias [377-380]. If the incision of the plate is deep, an inlay graft with inner preputial skin or buccal mucosa may be considered to reduce the risk of stenosis in primary repairs [381]. This also enables extension of the incision beyond the end of the plate to prevent meatal stenosis [382, 383]. For distal forms of hypospadias, a wide range of other techniques is available (Figure 4). The onlay technique using a preputial island flap is a good option for proximal hypospadias, or if the urethral plate is unsuitable for tubularisation [384]. Despite initial reports the use of TIP for proximal hypospadias repair is currently subject of debate.

If the continuity of the urethral plate cannot be preserved, single- or multi-staged repairs are used. Single-stage techniques include modifications of the tubularised flap (Duckett tube), such as a tube-onlay, an inlay-onlay flap or onlay flap on albuginea [385-387]. Alternatively, the Koyanagi-Hayashi technique is used [388-391]. Two (or more) staged procedures have become preferable over the past few years because of lower recurrence of ventral curvature and more favourable results, with variable long-term complication rates [382, 383, 385, 392-396].

Recent studies indicate that several techniques can characterise the incidence of urinary fistulas. Sufficient dissection and good tissue handling are essential. Further, adequate covering of the urethral reconstruction appears most important. The use of tunica vaginalis may yield better results than dartos fascia. If dartos fascia is used, a double-layer technique is recommended [397, 398]. New techniques for covering the neourethra are under investigation [399].

Figure 4: Algorithm for the surgical management of hypospadias



DSD = differences of sex development; Duckett = preputial hood onlay flap; GAP = glandular approximation procedure; MAGPI = meatal advancement and glanuloplasty incorporated; Mathieu = foreskin onlay flap; Snodgraft = preputial inlay graft; TIP = tubularised incised plate urethroplasty.

The choice of surgical technique is based on the severity of the urethral abnormality, as well as severity of curvature. If transection of the urethral plate is required for straightening, this influences the choice of urethral reconstruction.

*9.5.6 **Redo hypospadias repairs***

No definitive guidelines can be provided for redo hypospadias repair. All the above-mentioned procedures are used in different ways. It is essential to emphasise individualised treatment tailored to the specific needs of the patient and the anatomical status of the urethral plate and surrounding tissues.

*9.5.7 **Penile reconstruction following formation of the neo-urethra***

Following formation of the neourethra, 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 according to Cecil-Michalowski is used.

In countries in which circumcision is not routinely performed, preputial reconstruction can be considered if the prepuce is not required for urethral reconstruction or ventral skin coverage. It does not increase the risk of urethral complications, such as fistula formation, or the likelihood of reoperation [400]. This approach is considered a safe option, with a low risk of specific complications, such as preputial dehiscence (7-17%) and secondary phimosis (1.5%) [400-402]. In minor variants of hypospadias, isolated preputial reconstruction may be the procedure of choice to conceal the urethral malformation while avoiding the risks associated with urethroplasty.

9.5.8 Urine drainage and wound dressing

Urine is drained transurethral (e.g. dripping stent) or with a suprapubic tube. No drainage after distal hypospadias repair is another option [403, 404]. There is no strong evidence that the type of stent material (transurethral stents) impacts surgical outcome [405]. Similarly, there is no evidence that the type of dressing influences outcomes in hypospadias repair [406]. There is no consensus on optimal duration of stenting and dressing [403, 404, 406, 407].

Prophylactic antibiotics in hypospadias repair have not been shown to reduce the rate of postoperative surgical site infection or UTI, nor other long-term complications of surgery. The majority of evidence arises from distal hypospadias repair [408-410].

9.5.9 Analgesia (regional blocks)

Caudal blocks and peripheral nerve blocks (penile nerve blocks) are commonly used methods for perioperative analgesia in hypospadias surgery. All have been shown to have adequate postoperative analgesic properties [411-413]. The type of analgesic block has not shown to be associated with the risk of developing complications following primary hypospadias (all grades of hypospadias) correction in children [413-415].

9.6 Outcomes and complications

Outcomes in hypospadias repair are influenced by several key factors, including the severity of the condition, the patient's surgical history, the surgeon's experience and the surgical technique. Long-term follow-up is essential to assess both functional and aesthetic success, as well as to detect late complications.

9.6.1 Factors influencing outcomes

The following factors are known to influence outcomes:

- Severity of hypospadias: The complexity of the hypospadias plays a significant role in determining complication rates and the likelihood of success. Distal hypospadias repairs generally have high success rates, ranging from 85% to 90% in primary procedures [416]. On the other hand, proximal hypospadias presents a greater surgical challenge, with complication rates between 14% and 68%, reflecting the increased complexity of the condition [384, 417-419].
- Previous surgical history: Patients who require redo surgeries face a higher risk of complications such as urethral stricture and fistulas, largely due to scar tissue and reduced vascularity. The complication rate for redo surgeries is approximately 23.3%, compared to 12.2% for primary repairs [416].
- Surgeon experience: Surgeons with greater experience and higher surgical volumes consistently report fewer complications and improved long-term outcomes, especially in complex cases of proximal hypospadias The surgeon's preference and familiarity with the chosen technique can also influence the outcomes [368, 385, 420].
- Surgical technique: Different techniques yield varying outcomes and complications. For distal hypospadias, the TIP urethroplasty is a widely accepted technique with a low complication rate (below 10%) [416]. Tubularised incised plate urethroplasty repairs in distal hypospadias have fistula rates between 3% and 4%, similar to those seen with the Mathieu technique [381]. For proximal hypospadias, more-complex approaches are often required, and staged repairs are preferred. These show significantly lower overall complication rates (21% compared to 42% for one-stage repairs), including reduced risk of fistula (12% vs. 19%), meatal stenosis (8% vs. 17%) and urethral strictures (8% vs. 13%) [392, 418]. In severe cases requiring staged repairs using buccal mucosa grafts, complications such as graft fibrosis occur in more than one-third of patients following the second stage [396, 421, 422].

9.6.2 Complications

Overall, fistula rates range from 5% to 50%, depending on the complexity of the case [416, 417]. Glans size, specifically a width of less than 14mm, is an independent risk factor for urethral complications such as fistula formation as well as stenosis. Glans size should be considered when planning the surgical approach [407, 423]. Certain technical choices may reduce the chance of fistulas, such as the use of flaps to provide additional coverage of the neourethra (see Section 10.3 on management) [399, 417].

Meatal stenosis occurs in 5% to 15% of cases, particularly when the meatus is reconstructed under tension. The use of inlay grafts has been shown to reduce the risk of meatal stenosis by 66% compared to TIP alone, although these grafts do not significantly improve other long-term outcomes, such as fistula formation or glans dehiscence [381]. Urethral strictures occur in 8% to 13% of cases, especially in proximal hypospadias repairs. Even with two-stage procedures, strictures may still develop and require further surgical intervention in more-severe cases [399].

Recurrent penile curvature is a significant complication observed in proximal hypospadias repairs. Staged repairs have been shown to have lower risk of curvature recurrence than TIP in proximal hypospadias. Tubularised incised plate urethroplasty should only be performed in cases with no curvature or minimal curvature less than 30 degrees [368, 392, 424]. Additional surgeries to correct curvature may be needed as the child grows, particularly during puberty [392, 420, 425].

The incidence of glans and wound dehiscence ranged from 9% to 17%, with a higher likelihood in patients with more severe hypospadias. Small glans size, proximal meatal location, single-stage repairs and associated penile curvature are key risk factors for glans dehiscence following hypospadias surgery. Despite this, long-term functional outcomes are generally unaffected, although some patients seek aesthetic corrections [416, 426].

9.7 Long-term follow-up and transition

Long-term follow-up after hypospadias repair is essential, as significant rates of complications have been reported, which may occur early as well as several years after surgery [427, 428]. A recent study showed a total reoperation rate of 48% in the first fifteen years of life. This rate was highest in the subgroup of proximal hypospadias [400].

*9.7.1 **Voiding***

Obstructive urinary flow curves are frequently observed after hypospadias repair. While most children remain asymptomatic, conducting uroflow assesessments is essential during follow-up to monitor if the obstructive pattern worsens or becomes associated with lower urinary tract symptoms [429-431].

*9.7.2 **Penile appearance***

Various scoring systems for evaluating surgical outcomes and cosmetic satisfaction have been developed [432, 433]. Studies applying these scoring systems in postpubertal boys have revealed that caregivers and urologists express less satisfaction with penile appearance compared to the patients themselves. Moreover, many patients report equal satisfaction with the penile appearance compared to age-matched controls [433-436].

Differences in penile length compared to age-matched controls have correlated negatively to the overall patient satisfaction with penile appearance, especially in men with proximal hypospadias [437-439].

Studies on the long-term results of hypospadias repair are generally characterised by a high loss to follow-up, heterogeneous data, risk of selection bias and lack of validated measurement tools.

*9.7.3 **Sexual function and fertility***

Overall, studies have shown good self-reported sexual function and satisfaction with sexual life in adolescent boys and men following hypospadias repair during infancy. The severity of hypospadias and a high number of operations are key factors that may negatively influence psychosexual well-being [438, 440].

Lower paternity rates have been reported in men with hypospadias, particularly in severe cases and concomitant cryptorchidism, when comparing with healthy age-matched controls. The aetiology is multifactorial and may include the presence of persisting curvature, which can make intercourse with penetration difficult, reduced semen quality or ejaculation problems [438].

*9.7.4 **Health-related quality of life***

There is currently a lack of disease-specific, health-related quality of life (HRQoL) tools for hypospadias patients [441].

*9.7.5 **Transition***

See Chapter 27 on transitional urology.

9.8 Summary of evidence and recommendations for the management of hypospadias

Summary of evidence	LE
The suggested age at surgery for primary hypospadias repair is 6-18 months.	3
The therapeutic objectives are to correct the penile curvature, to form a neourethra of an adequate size, to bring the new meatus to the glans, and to achieve an overall acceptable cosmetic appearance and good function.	2b
The complication rates correlate with the severity of hypospadias and are not limited to childhood.	1a
Sexual function is usually well preserved.	2b

Recommendations	Strength rating
Differentiate isolated hypospadias from disorders of sex development at birth.	Strong
Counsel caregivers on functional and aesthetic value of hypospadias corrective surgery and possible complications.	Strong
Use the treatment algorithm (Figure 4) to select the most appropriate surgical technique.	Strong
Correct significant (>30 degrees) curvature of the penis.	Weak
Ensure long-term follow-up to detect urethral stricture, voiding dysfunction, recurrent penile curvature, ejaculation disorder and to evaluate patient´s satisfaction.	Strong

10. CONGENITAL PENILE CURVATURE

10.1 Epidemiology, aetiology and pathophysiology

Congenital penile curvature is penile bending of a normally formed penis with an orthotopic meatus. For penile curvature associated with hypospadias, refer to Chapter 9 on hypospadias. Ventral deviation is the most common type of congenital penile curvature (48%), followed by lateral (24%), dorsal (5%) and a combination of ventral and lateral (23%) [372, 442].

While the overall incidence of congenital penile curvature at birth is 0.6-5% [372], the incidence of clinically significant curvature is much lower. The extent of the curvature varies widely, as does the impact on the individual patient [368]. Congenital penile curvature can decrease sexual QoL in adults, and successful repair can restore patients' psychosocial and sexual wellbeing [443]. Curvature >30° is generally considered clinically significant, yet many patients with greater curvature may not experience problems [368].

Minor congenital penile curvature may simply be the result of ventral penile skin deficiency. This should be distinguished from more severe curvature due to asymmetry of the corpora cavernosa. Rarely, short urethra is the cause of congenital penile curvature.

10.2 Diagnostic evaluation

Congenital penile curvature is often not documented until later in childhood, because the penis only appears abnormal when erect. Patients are usually concerned with the aesthetic and/or functional aspects of their penis [444]. Detailed history, including sexual function, is important and photo documentation of the erect penis clearly showing the curvature from various angles is essential for optimal preoperative evaluation [445].

10.3 Management

Conservative management is the mainstay of treatment during childhood. Functional complaints are the main indication for surgery rather than the actual degree of penile curvature. Surgery can also be considered if the patient has cosmetic concerns. In general, it is reasonable to postpone surgery until an age at which the patient can decide. Age does not appear to affect the outcome [446].

Surgical correction of curvature aims to achieve corpora of similar size with the ultimate goal of patient satisfaction. The exact degree of curvature is determined at the time of surgery using an artificial erection test. The use of measurement tools aids in the accuracy of curvature assessment, particularly in moderate degrees of curvature [367].

Following assessment of curvature degree, the first step of surgery is degloving of the penile skin, followed by excision of any abnormal subcutaneous connective tissue, if present.

Correcting residual curvature may be achieved by shortening the dorsal, convex side of the curvature. Various techniques are in use for adapting the dorsal tunica albuginea, including wedge excision and closure (Nesbit procedure), plication without excision, and longitudinal incision with transverse closure (Heineke-Mikulicz principle).

All these methods incur the risk of postoperative shortening of the penis, the severity of which depends on the preoperative degree of curvature and the type of repair used [372]. A recent study showed loss up to 1cm in only 6% of patients with curvature >30 degrees [447]. The proportion of patients bothered by length reduction appears low [446, 448]. Altered sensation is also a concern with dorsal manipulation, particularly with mobilisation of the dorsal neurovascular bundle and may be transient [372, 448-450].

In rare cases in which dorsal shortening is not sufficient, ventral lengthening may be performed by urethral transection, corporotomies or corporoplasty with grafting. Refer to Chapter 9 for more details on hypospadias.

The overall success rate for correction of penile curvature is 90-100% in most series, although some studies accepted small degrees of residual curvature as straight [372, 448, 450]. Patient satisfaction rates are equally high [447].

10.4 Summary of evidence and recommendations for the management of congenital penile curvature

Summary of evidence	LE
Isolated congenital penile curvature with functional impairment is rare.	2a
Diagnosis is often made late in childhood.	2a
The penile curvature becomes apparent during erection.	1b
Congenital penile curvature can cause aesthetic as well as functional sexual problems.	1b

Recommendations	Strength rating
Ensure that a thorough medical history is taken, and a full clinical examination is carried out to rule out associated anomalies in boys presenting with congenital penile curvature.	Strong
Request photo documentation of the erect penis from various angles as a prerequisite in the preoperative evaluation.	Strong
Perform surgery if the penile curvature has functional implications.	Strong
Perform artificial erection at the beginning as well as at the end of surgery.	Strong

11. VARICOCELE IN CHILDREN AND ADOLESCENTS

11.1 Epidemiology, aetiology and pathophysiology

Varicocele is defined as an abnormal dilatation of testicular veins in the pampiniformis plexus caused by venous reflux. It is unusual in boys under ten years of age and becomes more frequent at the start of puberty. Varicocele is found in 14-20% of adolescents, with a similar incidence during adulthood. It appears mostly on the left side (78-93% of cases). Right-sided varicoceles are less common and are usually noted only when bilateral varicoceles are present and seldom occur as an isolated finding [451-453].

Varicocele develops during accelerated body growth and increased blood flow to the testes, by means of a mechanism that is not clearly understood. Genetic factors may be present [454, 455]. An anatomic abnormality leading to impaired venous drainage is expressed by the considerable prevalence of the left-side condition, in which the internal spermatic vein drains into the renal vein. Varicocele can induce apoptotic pathways due to heat stress, androgen deprivation and accumulation of toxic materials [456, 457]. In 70% of patients with grade

II and III varicocele, left-testicular volume loss was found. Abnormal reproductive hormonal levels (increased serum levels of FSH and LH and decreased levels of inhibin B) and semen quality were reported in varicocele patients and were directly related to varicocele severity [458-460]. Severe histological 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. Fertility problems will arise in approximately 20% of adolescents with varicocele [461]. The adverse influence of varicocele increases with time.

11.2 Classification systems

Varicocele is classified into three grades [462]:

- Grade I - Valsalva positive (palpable at Valsalva manoeuvre only);
- Grade II - palpable (palpable without the Valsalva manoeuvre); and
- Grade III - visible (visible at distance).

11.3 Diagnostic evaluation

Varicocele, being mostly asymptomatic, is generally noticed by the patient or caregivers 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. Clinical examination should include evaluation of the size of both testicles to detect a smaller testis.

In prepubertal boys and in isolated right varicocele, a renal US should be routinely added to rule out a secondary varicocele due to any retroperitoneal tumour extending into the renal vein and inferior vena cava.

Testicular volume is measured by US examination or by orchidometer. In adolescents, a testis that is smaller by >2mL or 20% compared to the other testis is considered hypotrophic [463]. Venous reflux into the plexus pampiniformis is diagnosed using Doppler US colour flow mapping in the supine and upright position and with the Valsalva manoeuvre [464]. Venous reflux detected in US only is classified as subclinical varicocele. Severity of reflux on Doppler US was shown to correlate with testicular damage [459].

Sperm analysis in principle allows assessment of testicular function, but the World Health Organization (WHO) parameters are not intended for prepubertal patients, and spontaneous improvements of abnormal sperm analyses has been observed in prepubertal patients [465]. Moreover, sperm analysis encounters cultural/ethical barriers in children [466]. Therefore, semen analysis in not widely used and is generally recommended only in older adolescents.

To assess testicular injury in adolescents with varicocele, supranormal FSH and LH responses to the luteinising hormone-releasing hormone (LHRH) stimulation test are considered reliable, because histopathological testicular changes have been found in these patients [467, 468].

11.4 Management

There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later and earlier diagnosis should not convey a more pressing need to intervene [469, 470]. Beneficial effect of pubertal screening and treatment for varicocele regarding the preservation of fertility and final chance of paternity is controversial [471-473]. The recommended indication criteria for correction for varicocele in children and adolescents are [452]:

- varicocele associated with a small testis (this should be confirmed during two subsequent visits performed six months apart), because asynchronous testicular growth can account for a temporary asymmetry, including in a considerable number of healthy adolescents [474].

Additional scenarios in which varicocele treatment can be considered on a case-by-case basis include:

- symptomatic varicocele [473]. Pain is present in 2-10% of varicoceles. The association between varicocele and pain is unclear and patients should be informed that pain can persist after varicocelectomy in 20% of cases [475];
- additional testicular condition affecting fertility such as a contralateral testicular condition;
- bilateral palpable varicocele;
- pathological sperm quality (in older adolescents); and
- cosmetic reasons related to scrotal swelling.

A reduced total testicular volume (left+right) in comparison with normal testes is a promising indication criterion, once the normal values are available [460, 469]. Repair of a large varicocele, causing physical or psychological discomfort, may also be considered. Other varicoceles should be followed up until a reliable sperm analysis can be performed.

*11.4.1 **Surgical management***

Surgical intervention is based on ligation or occlusion of the internal spermatic veins.

Ligation is performed at various levels:

- inguinal (or subinguinal) microsurgical ligation; and
- suprainguinal ligation, using open or laparoscopic techniques [476-479].

The advantage of inguinal (or subinguinal) microsurgical ligation is the lower level of 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) should be used because the internal spermatic artery is 0.5mm in diameter at the level of the internal ring [476, 478]. In a suprainguinal approach, an artery-sparing varicocelectomy may not offer any advantage in regard to catch-up growth and is associated with a higher incidence of recurrent varicocele [480, 481].

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 [476, 477, 482, 483]. The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs or suprainguinal open or laparoscopic lymphatic-sparing repairs [476, 478, 484, 485]. In suprainguinal open or laparoscopic lymphatic-sparing repairs, intrascrotal/intratesticular injection of isosulfan blue was recommended to visualise the lymphatic vessels [486, 487].

*11.4.2 **Radiological management***

Angiographic occlusion of the internal spermatic veins also meets the requirements of lymphatic sparing repair. It is based on retrograde or antegrade sclerotisation of the internal spermatic veins [488, 489]. However, although this method is less invasive and may not require general anaesthesia, it is associated with radiation burden, which is less controllable in the antegrade technique [452, 488, 489].

A low to moderate level of evidence exists showing that radiological or surgical treatment of adolescent varicocele is associated with improved testicular size/growth and sperm concentration. Several authors reported testicular catch-up growth after varicocelectomy in adolescents [490, 491]. An average proportion of catch-up growth of 76.4% (range: 52.6-93.8%) has been found according to a meta-analysis [492]. However, this may partly be attributable to testicular oedema associated with the division of lymphatic vessels [482]. Improvement in sperm parameters has been demonstrated after adolescent varicocelectomy [467, 493-495]. In one study, microsurgical varicocele repair in adolescents with varicocele significantly increases paternity rates and decreases time to conception postoperatively, but this must be confirmed in other series. The ultimate effects on fertility and paternity rates are not known [496].

The Panel conducted a systematic review and meta-analysis regarding the treatment of varicocele in children and adolescents [497]. Of 1,550 articles identified, 98 articles including 16,130 patients were eligible for inclusion (12 RCTs, 47 NRSs and 39 case series). The following paragraphs summarise the key findings.

The meta-analysis of the twelve RCTs revealed that varicocele treatment improved testicular volume (mean difference 1.52ml, 95% CI: 0.73-2.31) and increased total sperm concentration (mean difference 25.54, 95% CI: 12.84-38.25) when compared with observation. Lymphatic sparing surgery significantly decreased hydrocele rates ($p = 0.02$) and the OR was 0.08 (95% CI: 0.01, 0.67). Due to the lack of RCTs, it was not possible to identify a surgical technique as being superior to the others. It remains unclear whether open surgery or laparoscopy is more successful for varicocele treatment (OR ranged from 0.13 to 2.84).

The success rates of the treatment (disappearance of varicocele) were between 85.1% and 100%, whereas the complication rates were between 0% and 29% in the included studies. The most common complication reported was hydrocele. Resolution of pain after treatment was more than 90% in the reported series.

The major reason for varicocele recurrence is the persistence of branched spermatic veins that were not ligated during the initial repair. Treatment of recurrence is warranted only in those patients with clinical recurrence that show no improvement in testicular asymmetry or remain symptomatic. Treatment of recurrence can be surgical or by means of embolisation. A technique different from the primary repair is generally recommended to operate in a virgin field [498].

In conclusion, moderate evidence exists regarding the benefits of varicocele treatment in children and adolescents in terms of testicular volume and sperm concentration. Current evidence does not demonstrate superiority of any of the surgical/interventional techniques regarding treatment success. Lymphatic-sparing surgery significantly decreases hydrocele formation. Long-term outcomes, including paternity and fertility, remain unknown.

11.5 Summary of evidence and recommendations for the management of varicocele

Summary of evidence
Varicocele becomes more frequent at the onset of puberty and is found in 14-20% of adolescents.
Testicular problems are reported in up to 20% of patients, but the ultimate effect on paternity is unknown.
After adolescent varicocelectomy, left testis catch-up growth and improvement in sperm parameters has been demonstrated.
There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later.
Division of testicular lymphatics leads to hydrocele in up to 40% and to testicular hypertrophy. Lymphatic-sparing surgery significantly decreases hydrocele rates.

Recommendations	**Strength rating**
Examine varicocele in the standing position and classify into three grades.	Strong
Use scrotal ultrasound to evaluate testicular volume and to detect venous reflux in the supine and upright position and during Valsalva manoeuvre.	Strong
In all prepubertal boys with a varicocele and in all isolated right varicoceles, perform standard abdominal ultrasound to rule out a retroperitoneal mass.	Strong
Inform caregivers and patients and offer surgery for varicocele associated with a persistent small testis (size difference of >2mL or 20%).	Strong
Varicocele treatment can be also considered under the following circumstances: • symptomatic varicocele; • additional testicular condition affecting facility, such as a contralateral testicular condition; • bilateral palpable varicocele; • pathological sperm quality (in older adolescents); and • cosmetic reasons related to scrotal swelling.	Weak
Use some form of optical magnification (microscopic or laparoscopic magnification) for surgical ligation.	Strong
Use lymphatic-sparing varicocelectomy to prevent hydrocele formation.	Strong

12. URINARY TRACT INFECTIONS IN CHILDREN

12.1 Epidemiology, aetiology and pathophysiology

Urinary tract infections (UTIs) represent the most common bacterial infections in children [499-501]. The leading causative organism for UTIs is *Escherichia coli (E. Coli)*, but other bacteria have been increasing in prevalence. In a large European study, *E. Coli* was found in less than 50% of urine cultures. *Klebsiella pneumoniae, Enterobacter spp., Enterococcus spp., Pseudomonas spp., Proteus spp.* and *Candida spp.* have all become more frequent in nosocomial infections, but their prevalence has increased also for community-acquired infections [502]. In addition, an increase in the prevalence of beta-lactamase resistant *E. Coli* has been observed over the last decades, both in nosocomial and community-acquired UTIs [503, 504].

The pooled prevalence of UTI in children presenting with urinary symptoms is reportedly 7.8% (CI: 6.6-8.9) [505]. However, UTI prevalence and characteristics vary according to patient characteristics, such as age, sex and circumcision status in males. The prevalence is higher in neonates, where there is a male predominance, infections are more often caused by organisms other than *E. Coli* and there is a higher risk of urosepsis [505, 506]. In a retrospective study, 12.4% of blood cultures from neonates admitted for UTI were positive for bacteraemia [507], which is particularly common in nosocomial UTIs [507, 508]. One meta-analysis showed that, in children presenting with fever in the first three months of life, UTIs were present in 7.5% of girls, 2.4% (CI: 1.4-3.5) of circumcised boys and 20.1% (CI: 16.8-23.4) of uncircumcised boys [505]. The incidence for boys is highest during the first six months of life (5.3%) and decreases with age to approximately 2% for the ages up to six years. In girls, UTIs are less common during the first six months of life (2%) and incidence increases with age to around 11% for the ages up to six years [509]. Abnormal development of gut microbiota during infancy can also increase the risk of developing UTIs [510].

Urinary tract infections can determine the development of permanent focal renal damage, referred to as renal scarring, The risk of renal scarring increases if treatment of UTI is delayed [511], which is more often the case in older children than in younger infants [512] and in patients experiencing recurrent UTIs [513, 514]. The risk of renal scarring increases with the number of febrile UTIs, with an incidence of 2.8% after a first febrile UTI, rising to 25.7% after two febrile UTIs and 28.6% after three or more febrile UTIs [514]. The sum of multiple episodes of UTI may also lead to significant loss of renal function and the development of chronic renal failure [515]. Risk factors for recurrent UTIs include obesity, ethnicity, the presence of lower urinary tract disorders (LUTD) or bladder and bowel dysfunction (BBD), and any underlying urological conditions, particularly high-grade vesicoureteral reflux (VUR) [516-521].

Prompt treatment is important to prevent the development of renal damage with UTIs. However, the diagnosis is seldom certain, and misdiagnosis can lead to unnecessary treatment and medicalisation of otherwise healthy children [522, 523]. A systematic approach and management can significantly improve results [524-527].

12.2 Presentation symptoms

The most common presenting symptoms for UTI include fever, vomiting, lethargy and/or irritability. Urinary tract infection is the cause of fever in 4.1-7.5% of children who present to a paediatric clinic [528, 529].

Neonates with severe UTIs can present with non-specific symptoms, such as failure to thrive, jaundice and hyperexcitability, even in the absence of a fever. In neonates, it is important to rule out coexisting meningitis [530]. Septic shock is unusual, even in febrile cases.

Urinary symptoms are more common in children older than two years. These include frequent voiding, dysuria, and suprapubic, abdominal or lumbar pain.

12.3 Classification systems

All UTIs can eventually be classified into upper or lower urinary tract infections.

Lower UTIs (cystitis): An inflammatory condition of the urinary bladder mucosa with specific signs and symptoms including dysuria, frequency, urgency, malodorous urine, enuresis, haematuria and/or suprapubic pain.

Upper UTIs (pyelonephritis): A diffuse pyogenic infection of the renal pelvis and parenchyma. The onset of pyelonephritis is generally abrupt. Clinical signs and symptoms include fever (>38°C), chills, costovertebral angle or flank pain, and tenderness.

For clinical decision-making, however, the following classifications are possibly more relevant.

*12.3.1 **Classification according to clinical presentation***

From a clinical point of view, UTIs can be differentiated into febrile and nonfebrile.

Febrile UTIs (fUTIs)s: Usually involve the upper tract, but mild fever can sometimes occur also in lower urinary tract infections. These are the UTIs of greatest interest in terms of the risk of developing renal damage.

Nonfebrile UTIs: Infections generally limited to the lower urinary tract. Lower urinary tract symptoms are typically present. Infants and children may present with non-specific signs such as poor appetite, failure to thrive, lethargy, irritability, vomiting or diarrhoea.

A nonfebrile UTI should be differentiated from an asymptomatic bacteriuria, where there is a positive culture in an otherwise asymptomatic child.

*12.3.2 **Classification according to episode: first, recurrent, breakthrough***

A UTI can occur as first episode or a recurrence. A breakthrough infection is a UTI in patients on continuous antibacterial prophylaxis. A breakthrough UTI is usually due to bacteria resistant to the antibiotic used for prophylaxis and is also associated with parental non-compliance and/or severe underlying urogenital anomalies [531, 532].

*12.3.3 **Classification according to age and toilet-training status***

Urinary tract infection can occur in infants, in children during the period of toilet training, in toilet-trained children and finally in older patients. Infants represent a critical group as the diagnosis of UTI can be difficult, the course severe and UTI can be the first sign of a previously unknown urinary tract abnormality. Urinary tract infection can occur during toilet training as a result of transitory partial bladder control during this period. These infections tend to be mild and generally do not recur. Urinary tract infections in toilet trained patients can suggest an underlying LUTD/BBD. Urinary tract infections in older patients, particularly in females, can be associated with sexual intercourse.

*12.3.4 **Classification according to the clinical course***

This is particularly relevant during a first UTI. Children may have typical or atypical UTIs. Typical UTIs are due to common bacteria, generally *E. Coli*. The UTI responds quickly to oral antibiotics (within 48 hours), and symptoms and patient conditions are not severe enough to require hospital admission. In contrast, atypical UTIs are generally due to bacteria other than *E. Coli* and/or multiresistant bacteria. The patient fails to respond to oral treatment or is unable to tolerate oral treatment, and hospital admission may be required.

*12.3.5 **Classification according to urinary tract abnormalities***

Most UTIs occur in patients without any underlying urinary tract abnormalities, and with normal renal function and a competent immune system. Under these circumstances, the UTIs is usually typical and the need for additional imaging is controversial.

At the opposite end of the spectrum, UTIs can occur as a complication in a child with a known abnormality of the urinary tract, including any prenatal history of urinary tract dilatation. These are usually fUTIs. Common urinary tract abnormalities that can increase the risk of UTI include posterior urethral valves, strictures, stones, LUTD of either neurogenic or non-neurogenic origin, and VUR. This category also includes patients developing a UTI after urinary tract surgery, particularly those with indwelling stents/catheters and/or after renal transplantation [533, 534].

Finally, UTIs can be the presenting symptoms of a previously unknown urinary tract condition. These are usually fUTIs.

12.4 Diagnostic evaluation

*12.4.1 **Medical history***

History taking should define the type of episode: first or recurring; possible history of urinary tract abnormalities, including any dilatation detected during prenatal US screening; prior operations; family history; and the presence of lower urinary tract symptoms (LUTS) and/or constipation.

12.4.2 ***Physical examination***

Physical examination includes a general examination to exclude other causes of fever. Assessment of body weight and temperature, the abdomen (constipation, palpable and painful kidney, or palpable bladder), flank, lower back (stigmata of spina bifida or sacral agenesis) and genitalia (phimosis, labial adhesions, vulvitis, epididymo-orchitis) should be performed.

12.4.3 ***Urine sampling, analysis and culture***

Urine must be collected under defined conditions and investigated as soon as possible to confirm or exclude a UTI, especially in children with a fever. Urine sampling must be performed before any antimicrobial agent is administered. The technique for obtaining urine for urinalysis, as well as culture method, affects the rate of contamination, which influences interpretation of the results. This can be challenging in early infancy and depends on the method of urine sampling [535].

In older, toilet-trained children who can void on command, after carefully retracting the foreskin and cleaning the glans penis in boys and spreading the labia and cleaning the periurethral area in girls, the use of a clean catch, especially a midstream urine, can be an acceptable technique for obtaining a reliable urine sample. In a randomised trial, cleaning the urethral meatus and perineum twice with gauze and liquid soap reduced the risk of sample contamination from 23.9% (41/171) to 7.8% (14/171) [536].

In neonates, infants and non-toilet-trained children, there are four main methods with varying contamination rates and invasiveness with respect to urine collection:

(1) Plastic bag attached to the cleaned genitalia: Although this technique is most often used in daily practice, contamination rates are high: approximately 50-60% [537]. The technique is only deemed to be reliable when culture results are negative. If the dipstick is negative for both leukocyte esterase and nitrite, or microscopic analysis is negative for both pyuria and bacteriuria, UTI can be excluded without the need for confirmatory culture [538].

(2) Clean-catch urine (CCU) collection: There appears to be a good correlation between the results of urine cultures obtained using this method and suprapubic aspiration (SPA), with a false-positive rate of 5% and false-negative rate of 12% [539, 540]. However, the contamination rate is higher for CCU of up to 26% compared to catheterisation (10%) and suprapubic bladder aspiration (1%) [537, 541]. In one prospective cohort study of infants below the age of six months, the success rate was 49% and the contamination rate 16%, with some differences in culture results between those obtained by CCU and those by more invasive methods [542].

(3) Transurethral bladder catheterisation is the fastest and safest method to obtain a reliable urine sample for microscopic and bacteriological evaluation to rule out - or to document - a UTI in non-toilet-trained infants and children.

(4) Suprapubic bladder aspiration is the most invasive modality but also the most sensitive method to obtain an uncontaminated urine sample in this age group [543, 544].

12.4.3.a **Urinalysis**

Three methods are commonly used for urinalysis:

(1) Dipstick: This method is appealing because it provides rapid results, does not require microscopy and is ready-to-use. Leukocyte esterase (as a surrogate marker for pyuria) and nitrite (which is converted from dietary nitrates by most Gram-negative enteric bacteria in the urine) are the most frequent markers and are usually combined in a dipstick test. The conversion of dietary nitrates to nitrites by bacteria takes approximately four hours in the bladder [540, 545]. The sensitivity of using nitrate alone to screen febrile children < 2 years of age is too low, and relevant UTIs can be missed. However, the specificity is high for children at any age [546, 547]. In febrile infants < 90 days old, urine dipstick tests from CCU samples can be used for screening of UTIs when nitrites and leukocyte esterase are used in combination, with a sensitivity of 86% and a specificity of 80% [548, 549]. Anand *et al.* (2023) assessed the use of urine dipstick tests for the rapid detection of UTIs in children, demonstrating a sensitivity of 75% and a specificity of 90%, suggesting their utility in resource-limited settings [550].

(2) Microscopy: This is the standard method of assessing pyuria after urine centrifugation with a threshold of five white blood cells (WBCs) per high-power field (25 WBC/µL) [551]. In uncentrifuged urine, >10 WBC/µL has been demonstrated to be sensitive for UTI [552], and this performs well in a hospital setting [553]. However, this is rarely done in an outpatient setting. No significant differences were found between dipsticks and microscopy testing for UTI [547]. A meta-analysis showed that only microscopy with Gram staining has a higher sensitivity compared to dipsticks [554].

(3) Flow imaging analysis technology: This technology is increasingly being used to classify particles in uncentrifuged urine specimens [555]. The numbers of WBCs, squamous epithelial cells and red cells correlate well with those found by manual methods [540]. Flow cytometry-based bacterial and leukocyte count analysis when using a cut-off value of 250 bacteria/µL in the presence of leukocyturia has a sensitivity of 0.97 and specificity of 0.91 for diagnosing UTIs [556].

In addition to these methods, urine biomarkers are currently under evaluation to distinguish UTIs from culture-negative pyuria. Their use, however, is still not in routine clinical practice [557-559].

12.4.3.b Urine culture

Following negative results for dipstick, microscopic or automated urinalysis, urine culture is generally not necessary, especially if there is an alternative source of fever. If the dipstick result is positive, confirmation by urine culture is strongly recommended.

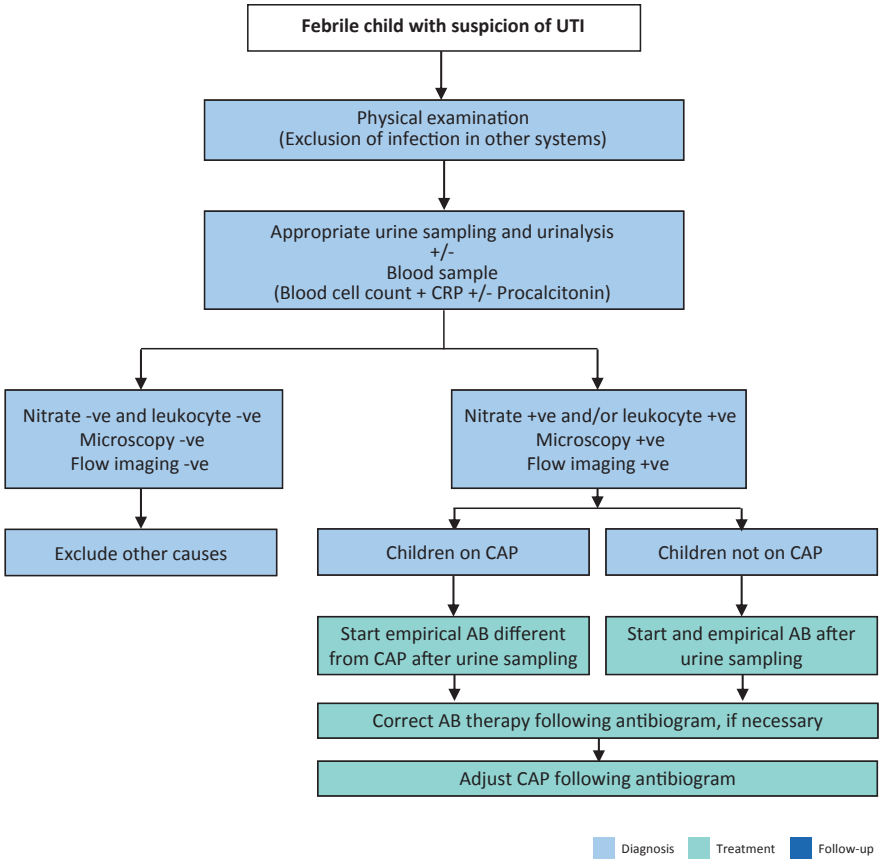
The question of what number of colony-forming units (CFUs) should be used as a cut-off to diagnose a UTI is still controversial. In patients with a fUTI, $\geq 10^5$ cfu/mL can be expected. However, the count can vary and be related to the method of specimen collection, diuresis, and time and temperature of storage until cultivation occurs [506]. Clean-catch urine, midstream and catheterisation urine cultures can be considered positive as 10^3 - 10^4 cfu/mL in a monoculture, and any counts obtained after SPA should be considered significant. Mixed cultures are indicative of contamination. In febrile children < 4 months of age, a cut-off value of 10^3 cfu/mL can be used when clinical and laboratory findings match and a correct sampling method has been used [560].

A negative culture with the presence of pyuria may be due to incomplete antibiotic treatment, urolithiasis, or foreign bodies in the urinary tract, and infections caused by *Mycobacterium tuberculosis* or *Chlamydia trachomatis*.

*12.4.4 **Blood tests***

Blood tests are a complement for the diagnosis of UTI and are generally performed only in patients requiring hospital admission. In cases of renal parenchymal involvement, a neutrophilic leukocytosis is expected, as is a rise in C-reactive protein. These markers are non-specific and several additional markers are under evaluation, but are not used in clinical practice [558, 561]. In current clinical practice, the most specific blood marker of renal involvement is procalcitonin [562]. A cut-off value of serum procalcitonin >1.0ng/mL has been shown to be predictive of acute pyelonephritis in young children [563]. In patients with febrile UTIs requiring admission, serum electrolytes and blood cell counts should also be requested.

Figure 5: Diagnostic evaluation and subsequent management of a febrile child with suspicion of UTI



AB = antibiotic; CAP = continuous antibiotic prophylaxis; CRP = C-reactive protein.

12.5 Additional workup

Imaging modalities in the acute phase of the infection should be differentiated from follow-up investigations recommended in patients following a first or recurrent episode of UTI.

*12.5.1 **Ultrasound (US)***

The Panel recommends a renal and bladder ultrasound (US) in children with febrile UTIs to rule out urinary tract abnormalities. The investigation should be performed within 24 hours in infants and acutely ill children, as these patients are typically hospitalised and may require urgent management. However, in children who do not require hospitalisation, renal US may be scheduled at a later date. In toilet-trained patients, the US should be performed before and after voiding to assess upper tract changes in relation to bladder filling and to measure post-void residual (PVR) urine volumes, which can be the sign of underlying voiding dysfunction. An elevated PVR urine volume predicts the recurrence of UTIs in toilet-trained children [564]. Ultrasound can also help in assessing the presence of faecal impaction [565].

Overall, abnormal results are found in 15% of cases [538], and 7% require further investigations [566]. A study evaluating the necessity of performing US only in children with a pathogen other than *E. Coli* during their first UTI or those experiencing recurrent UTI demonstrated that this selective approach could reduce the overall number of ultrasound scans by 40.4% [567].

The overall accuracy of US in predicting high-grade VUR is low, with a sensitivity 0.59 (CI: 0.45-0.72) and specificity 0.79 (CI: 0.65-0.87) [568]. When perirenal or psoas abscesses or renal masses are seen on US, it is important to consider xanthogranulomatous pyelonephritis, and subsequent CT scan is recommended [569].

*12.5.2 **Radionuclide scanning/MRI***

Dimercaptosuccinic acid (DMSA) scan is the most accurate method to document localisation of a UTI to the renal parenchyma and the associated renal scarring that can ensue.

To assess renal involvement, the DMSA scan must be performed within days of a febrile UTI (acute or early DMSA). The pyelonephritis appears as a perfusion defect within the kidney. These changes were found to correlate with the presence of dilating reflux, the risk of further pyelonephritis episodes, breakthrough infections, and the development of renal scarring [570]. After the first community-acquired fUTI, it has been shown that the majority of renal units with dilating VUR had normal early DMSA scanning [571]. The sensitivity of the DMSA scan to detect VUR is 0.75 (CI: 0.67-0.81) with a specificity of 0.48 (CI: 0.38-0.57), and a negative DMSA scan results in a very low probability of high-grade VUR [572]. This investigation, however, is no longer widely used in clinical practice to limit the level of radiation exposure in patients.

Dimercaptosuccinic acid scans are generally recommended in the follow-up of febrile UTIs, after a period of at least six months from the infection, to detect persistent scaring [573].

Increasingly physicians tend to avoid DMSA scans after the first fUTI, if the US does not demonstrate any pelvicalyceal dilatation, or cortical abnormalities.

Diffusion-weighted MRI has also been shown to accurately diagnose acute pyelonephritis and reveal late renal scars and could be an alternative to DMSA, therefore, avoiding radiation burden [574]. Magnetic resonance imaging, however, cannot be considered standard practice at present.

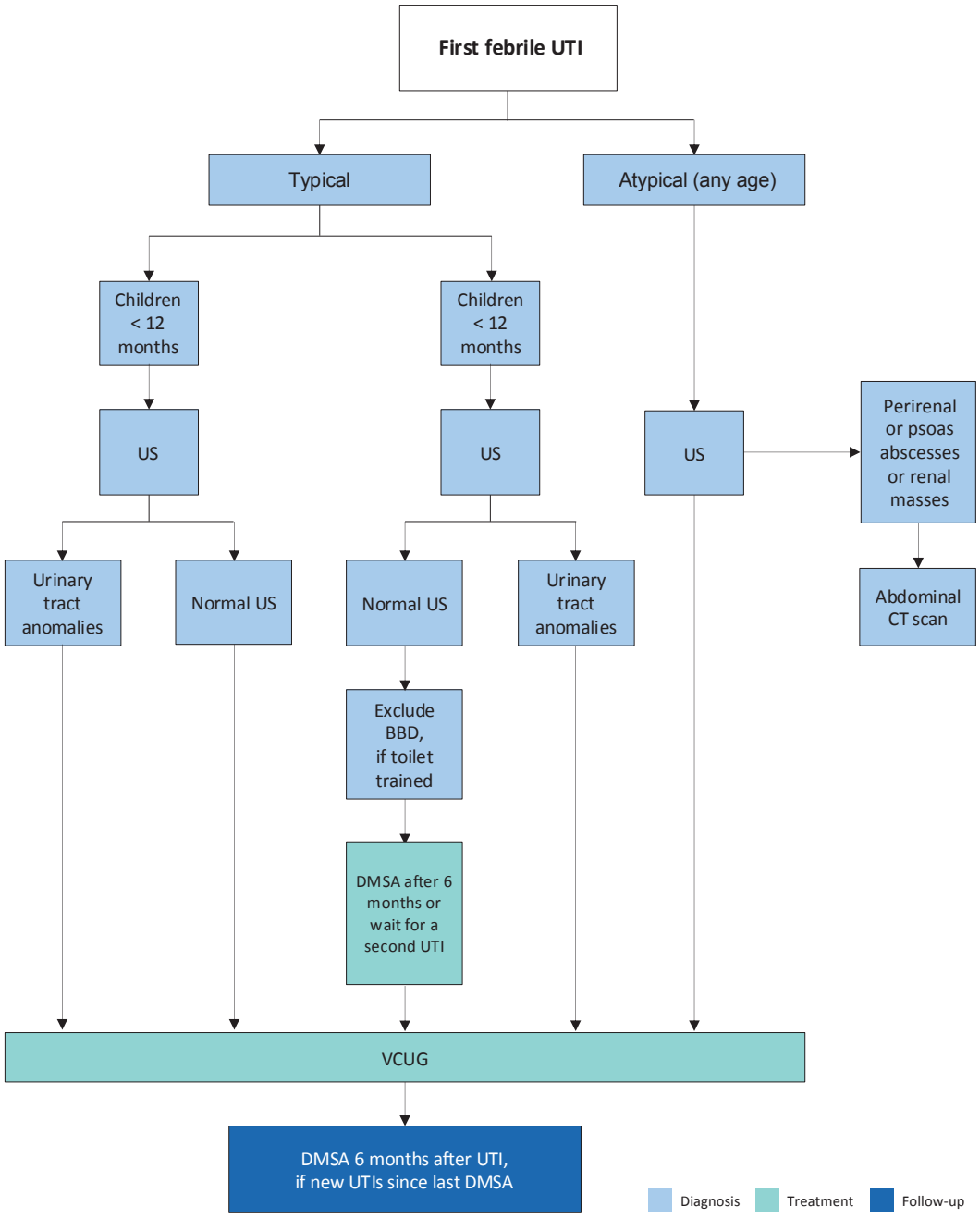
*12.5.3 **Voiding cystourethrography/urosonography***

Voiding cystourethrography (VCUG) is the imaging of choice to detect VUR. The timing of VCUG does correlate with the presence or severity of VUR [575]. Performing a VCUG close to the UTI in patients with proven sterile urine does not cause any significant morbidity [576]. Using harmonic voiding urosonography may be an alternative to standard VCUG avoiding radiation [577, 578]. Visualisation of the urethra may be difficult with this technique. Neither examination, however, is recommended in the acute phase of the UTI and, given the fact that the investigation is invasive and bothersome for the family [566, 579], selective use is generally recommended during follow-up. VCUG is recommended in the following cases: (1) first febrile UTI in infants under 12 months, regardless of ultrasound results; (2) recurrent febrile UTI, abnormal ultrasound or presence of an abnormal DMSA in a top-down approach; and (3) atypical UTI at any age, regardless of ultrasound results. [16, 580].

Prediction models using machine learning have also been developed to combine additional factors [581]. As an alternative strategy to avoid unnecessary VCUG investigations, VCUGs can be limited to patients with an abnormal DMSA. This is known as a top-down approach. Numerous top-down strategies have been proposed, but waiting for a second infection can be an alternative option in patients with typical infections and a normal US. The Panel recommends the diagnostic flowchart depicted in Figure 6 [582].

In some patients with recurrent febrile UTIs and an abnormal DMSA, but a VCUG showing no reflux, a cystography performed with endoscopic instillation of the contrast in front of the ureteral orifice (positional instillation of contrast [PIC] cystography), which may demonstrate reflux [583].

Figure 6: Diagnosis strategy for first febrile UTI



BBD = bladder and bowel dysfunction; CT = computed tomography; DMSA = dimercaptosuccinic acid; US = ultrasound; UTI = urinary tract infections; VCUG = voiding cystourethrogram.

12.6 Management

The cornerstone in the management of UTIs is the administration of antimicrobial therapy and should not be delayed. Delaying treatment in children with a febrile UTI for more than 48-72 hours increases the risk of renal scars [511, 572]. Supportive treatment may be required in severely ill patients.

Temporary urinary diversion can be considered on a case-by-case basis. The requirement for surgical procedures, such as cutaneous ureterostomy or nephrectomy, during the acute phase is exceptional. After the treatment of the infection, it is crucial to address any LUTD/BBD, if present [584-587].

*12.6.1 **Administration route of antibacterial therapy***

The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; noncompliance; and complicated pyelonephritis (e.g. urinary obstruction).

As a result of the increased incidence of urosepsis and severe pyelonephritis in newborns and infants aged less than two months, parenteral antibiotic therapy is recommended in this age group. Electrolyte disorders with life-threatening hyponatraemia and hyperkalaemia based on pseudohypoaldosteronism can also occur in these patients [588, 589].

The choice of agent is also based on local antimicrobial sensitivity patterns and should later be adjusted according to sensitivity testing of the isolated uropathogen [540]. Not all available antibiotics are approved by national health authorities, especially in infancy. When recent urinary cultures are available, the sensitivity pattern should guide in the choice of treatment. Consider local resistance patterns and patient kidney function in the choice of antibiotic treatment.

*12.6.2 **Adjustment of antimicrobial agents***

There is a large heterogeneity in the prevalence of antibiotic resistance patterns of uropathogenic *E. Coli* within different countries, with increased high resistance patterns in countries outside of the Organisation for Economic Co-operation and Development (OECD) [590]. There are increasing reports of UTIs caused by extended spectrum ß-lactamase-producing *enterobacteriaceae* (ESBL) in children, with pooled numbers of UTI caused by ESBL-producing bacteria of approximately 14% [591]. Within OECD countries, the prevalence of resistance was 53% for ampicillin, 24% for trimethoprim, 8% for co-amoxiclav, 2% for Ciproxin and 1% for nitrofurantoin [590]. According to Al-Wandawy *et al.* (2023), nearly all bacteria isolated from children with UTI showed resistance to ampicillin (65.62%) and amoxicillin (65.62%), but demonstrated high sensitivity to nitrofurantoin (90%), cefoperazone-sulbactam (85%) and meropenem (92%) [592]. Several risk factors and determinants for UTIs caused by ESBL and non-*E. Coli* bacteria have been identified, including a history of infection, recent hospitalisation, short-term exposure to antibiotics, and prophylaxis [590, 593, 594]. Overall, oral nitrofurantoin appears to be a good empirical choice in the treatment of cystitis [595].

The choice of antibiotics should be guided by good antibiotic stewardship. It is important to be aware of local resistance patterns, which are variable between countries and even between hospitals. Local antibiogram protocols and web-based recommendations can guide the choice of the type of antibiotic therapy. The individual patient's previous urine cultures should also be taken into account in these decisions. The daily dosage of antibiotics is dependent on the age and weight of the child, as well as on renal and liver function (see Figure 5).

*12.6.3 **Duration of therapy***

Prompt, adequate treatment of UTI can prevent the spread of infection and renal scarring. In newborns and young infants with a febrile UTI, up to 20% may have a positive blood culture [507, 596]. Children with bacteraemia did not show significant clinical differences with non-bacteraemic infants but did receive longer parental treatment [597]. In late infancy, there are no differences between strategies regarding the incidence of parenchymal scars, as diagnosed with DMSA scan [598]. The duration of antibiotic therapy should be determined by the nature of the UTI, with simple cystitis generally requiring shorter courses, while febrile and complicated infections may necessitate longer treatment [540]. However, a simple cystitis can be treated with three to five days of antibiotics [599]. No significant difference in recurrent UTIs and rehospitalisation was found between seven-day parental treatment and longer regimens for bacteraemic UTIs in younger infants [600, 601]. In young infants, a short course of parental treatment with early conversion to oral antibiotics may be considered [602]. The short course therapy for urinary tract infections (SCOUT) randomised trial demonstrated that a five-day course of oral antibiotics was noninferior to a ten-day course for the treatment of uncomplicated UTIs in children, supporting the use of shorter regimens when clinically appropriate. However, febrile UTIs still require longer courses to reduce the risk of recurrence and renal complications [603]. The use of exclusively oral therapy with a third-generation cephalosporin (e.g. cefixime or ceftibuten) has been demonstrated to be equivalent to the usual two to four days intravenous therapy followed by oral treatment [604-607]. Similar data have been shown for amoxicillin-clavulanate [608]. If ambulatory therapy is chosen, adequate surveillance, medical supervision and, if necessary, adjustment of therapy must be guaranteed. In the initial phase of therapy, close contact with the family is advised [609].

In complicated UTIs, uropathogens other than *E. Coli.*, such as *Proteus mirabilis, Klebsiella spp., Pseudomonas aeruginosa, enterococci* and *staphylococci* are the most likely causative pathogens [596]. Children with acute focal bacterial nephritis often present without pyuria and significant bacteriuria. For most children, the pathogenesis is related to ascending infection due to a pre-existing uropathy, especially VUR or urinary obstruction. Initial management consists of broad-spectrum antibiotics with good tissue penetration. A treatment regimen of a total of three weeks with initial intravenous and subsequently oral therapy tailored to the pathogen identified in culture is recommended [610].

*12.6.4 **Adjunct steroid treatment***

Adjuvant dexamethasone treatment, by modulating the immune response, has been hypothesised to reduce kidney scarring after acute pyelonephritis in children. A multicentre, prospective, double-blind, placebo-controlled, randomised clinical trial demonstrated no difference either in the duration of the UTI or in the presence of renal scars on a DMSA performed six months after the infection, between patients receiving a three-day course of either intravenous dexamethasone 0.30mg/kg/day twice daily or placebo [611].

*12.6.5 **Temporary urinary diversion***

Temporary bladder drainage via a transurethral catheter or a suprapubic cystostomy might be required in case of failure to respond to treatment with suitable antibiotics within 72 hours. It can offer some advantages in selected patients with urinary tract abnormalities, underlying medical conditions, poor urine flow, abdominal or bladder mass, elevated creatinine levels, significant kidney damage and septicaemia. Drainage of infected urine may prevent progression to renal abscess formation and preserve renal function. In patients affected by refractory UTIs unresponsive to antibiotic treatment and concomitant obstructive uropathy, temporary urinary diversion via a ureteral stent or a nephrostomy can be considered.

*12.6.6 **Monitoring***

With successful treatment, urine usually becomes sterile after 24 hours, and leukocyturia normally disappears within three to four days. Normalisation of body temperature can be expected within 24 to 48 hours following the commencement of therapy in 90% of cases. In patients with prolonged fever and those failing to respond, treatment-resistant uropathogens or the presence of congenital uropathy or acute urinary obstruction should be considered. Repeated US examination is recommended in these cases.

12.7 Measures to prevent UTI recurrences

Recurrent UTIs are problematic as the symptoms are bothersome to children, and recurrent febrile UTIs may also result in renal scarring [514]. Therefore, it is important to prevent the incidence of recurrent UTIs.

*12.7.1 **Chemoprophylaxis***

Chemoprophylaxis is commonly prescribed to prevent UTIs in children. However, with increasing rates of bacterial resistance, the question of which patients should receive antibacterial prophylaxis should be carefully considered. The evidence for the use of antibacterial prophylaxis has been conflicting. Its use causes a reduction of the number of recurrent symptomatic UTIs, but long-term use of antibacterial prophylaxis has also been associated with increased microbial resistance [531, 612]. The use of antibacterial prophylaxis did not reduce newly acquired renal damage in children after the first or second UTI [612]. However, when used in patients with anatomic abnormalities of the urinary system, a reduction in UTIs and subsequent renal scarring has been shown [531, 612]. A prospective multicentre study demonstrated that a ureteral diameter of 7mm or greater indicates a higher risk of UTI, and that these patients may benefit from chemoprophylaxis administration [613]. The Panel recommend chemoprophylaxis for the first year of life in patients with evidence of megaureter. In children with LUTD/BBD and VUR, a benefit was seen in the reduction of recurrent UTI with the use of antimicrobial prophylaxis [8] (see also Chapter 17 on vesicoureteric reflux). Chemoprophylaxis can be considered under these circumstances, particularly while waiting for the treatment of the LUT dysfunction to become effective. For the specific group of patients with incomplete bladder emptying with properly performed clean intermittent catheterisation but still suffering from recurrent UTIs, the intravesical application of gentamycin has proven to be effective [614, 615].

Table 1: Drugs for antibacterial prophylaxis*

Substance	Prophylactic dosage (mg/kg bw/d)	Limitations in neonates and infants
Trimethoprim**	2	Not recommended under six weeks of age
Trimethoprim and Sulfamethoxazole	1-2	Not recommended under two months of age
Sulfamethoxazole	1-2	Up to three months of age
Nitrofurantoin**	1-2	Not recommended under two months of age
Cefaclor	10	No age limitations
Cefixim	2	Preterms and newborns

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*** Substances of first choice are nitrofurantoin and trimethoprim. In exceptional cases, oral cephalosporin can be used.*

12.7.2 ***Nonantibiotic prophylaxis***

The most investigated nonantibiotic prophylactic measures to prevent UTI recurrence in children are cranberry products and probiotic. As reported in a recent systematic review and meta-analysis of randomised controlled trials, both these interventions reduced the risk of UTI recurrence as compared with placebo in children with a normal urinary tract. The quality of evidence is moderate for cranberry, whereas the quality of evidence for probiotics products must be strengthened with larger and more robust trials [617]. The results for probiotics are somewhat more conflicting, with one systematic review not ruling out any effect [618] and an RCT showing promising results in children with normal urogenital anatomy [619]. A meta-analysis could not demonstrate a beneficial effect, and therefore probiotics should be used only as an adjuvant to antibiotic prophylaxis [620, 621].

Other supplements of interest include vitamin A, which has shown promising results in preventing renal scarring in children with acute pyelonephritis [622, 623]. The use of vitamin E could potentially improve the symptoms of UTI [624]. Several studies have demonstrated that vitamin D deficiency could be a risk factor for renal scarring in patients with recurrent UTIs. Vitamin D treatment may be beneficial for preventing renal scarring in patients with recurrent UTIs, but no prospective studies have been conducted [625]. None of these supplementations, however, can be considered at present for routine use in clinical practice.

12.7.3 ***Phimosis***

When a physiologic phimosis is present in boys with a UTI, the use of steroid cream can significantly reduce recurrent UTIs [51]. The number needed to treat to prevent a single UTI is high in patients without associated urinary tract abnormalities, which calls into question the actual cost-to-benefit ratio [49]. Circumcision appears to be more cost-effective in preventing UTI recurrences in patients with posterior urethral valves (PUV) and vesicoureteral reflux (VUR) [626, 627] (see also Section 21.1 on posterior urethral valves).

12.7.4 ***Bladder and bowel dysfunction and lower urinary tract disorders***

Bladder and bowel dysfunction (BBD) and lower urinary tract disorders (LUTDs) are risk factors for which every toilet-trained child with UTIs should be screened at presentation [517]. Normalisation of micturition disorders or bladder overactivity is important to lower the rate of UTI recurrence. In case of signs of BBD during infection-free intervals, further diagnosis and effective treatment are strongly recommended [628]. Exclusion of BBD is strongly recommended in any toilet-trained child with febrile and/or recurrent UTIs, and it should be treated (for treatment, see Chapter 13 on day-time lower urinary tract conditions). Treatment of constipation leads to a decrease in UTI recurrence, and a multidisciplinary approach is recommended [517, 628-630].

The importance of comprehensive and preventive management of UTIs in patients with LUTD cannot be underestimated. Adequate hydration and proper hygiene, along with the evaluation and treatment of bladder dysfunctions, are key measures to reduce the recurrence of these infections. Similarly, optimisation of bladder emptying and correct catheterisation techniques in patients with neurogenic bladder dysfunction is critical to prevent UTI recurrence (for treatment, see the new guideline on spinal dysraphism in children and adolescents) [631, 632].

12.8 Summary of evidence and recommendations for the management of UTI in children

Summary of evidence	LE
Urinary tract infection (UTI) represents the most common bacterial infection in children less than two years of age. The incidence varies depending on age and sex.	1b
Urinary tract infections, particularly if febrile and/or recurrent, can cause renal scarring.	1b
Urinary tract infections are classified according to upper and lower urinary tract involvement, clinical presentation, episode, severity, age and toilet-training status, clinical course, and associated urinary tract abnormalities.	2b
Urinalysis by dipstick yields rapid results but should be used with caution and in a clinical context. Microscopic investigation is the standard method of assessing pyuria after centrifugation.	2a
The number of colony forming units (CFUs) in the urine culture can vary, however, any colony count of one organism indicates a high suspicion for UTI.	2b
Prompt treatment of febrile UTIs reduces the risk of developing renal scarring.	1b
Due to increasing resistance numbers, good antibiotic stewardship should guide the choice of antibiotics, taking into account local resistance patterns, previous urine cultures (when available) and clinical parameters.	2a

Preventive measures against recurrent UTIs include chemoprophylaxis, cranberries and probiotics.	1b
Some studies suggest potential benefits of vitamin A, E and D supplements in preventing UTIs.	2a
Treatment of bladder and bowel dysfunction and lower urinary tract dysfunction reduces the risk of UTI recurrences.	1b

Recommendations	Strength rating
Take a detailed medical history, assess clinical signs and symptoms, and perform a physical examination in the evaluation of children suspected of having a urinary tract infection (UTI).	Strong
Use bladder catheterisation or suprapubic bladder aspiration to collect urine for urinalysis and cultures in non-toilet-trained children.	Strong
Use clean catch urine for screening for UTI in non-toilet-trained children.	Weak
Do not use plastic bags for urine sampling in non-toilet-trained children.	Strong
Use midstream urine in toilet-trained children for analysis and culture.	Strong
Perform renal and bladder US within 24 hours in infants with febrile UTI and acutely ill children to check for abnormalities of the urinary tract.	Strong
Consider a voiding cystourethrogram (VCUG) in the follow-up of patients developing febrile UTI < 1 year of age, with atypical infections, with recurrent infections, or with ultrasound abnormalities.	Weak
Consider a dimercaptosuccinic acid (DMSA) scan at least six months after a febrile UTI to assess kidney function and the presence of renal scars.	Weak
Treat febrile UTIs with four-to-seven-day courses of oral or parenteral therapy.	Strong
Chose parenteral therapy in severely ill patients or if oral treatment is not tolerated.	Strong
Start empirical antibiotic therapy for complicated febrile UTI.	Strong
Consider urinary drainage in patients with UTIs unresponsive to antibiotic treatment.	Weak
Offer antibacterial prophylaxis in patients at risk of recurrent UTIs.	Strong
Consider dietary supplementation as an alternative or add-on preventive measure in selected cases.	Weak
Offer treatment for phimosis to patients with underlying urological conditions.	Weak
Assess bladder and bowel dysfunction and lower urinary tract function in any toilet-trained child with febrile and/or recurrent UTI and treat it.	Strong

13. DAYTIME LOWER URINARY TRACT CONDITIONS

13.1 Terminology, classification, epidemiology and pathophysiology

Normal storage and emptying of the bladder at a socially accepted place and time is mostly achieved by age three to four. Children with LUT conditions would present with failure to achieve continence (being still wet after the age of four), urgency, weak stream, hesitancy, frequency and accompanied UTIs. Isolated night-time wetting without any daytime symptoms is known as 'enuresis' and considered as a different entity [633] (See Chapter 14).

Urinary incontinence in children may be caused by congenital anatomical or neurologic abnormalities such as ectopic ureter, bladder exstrophy or myelomeningocele (MMC). In many children, however, there is no such obvious cause for the incontinence, and they are referred as having functional bladder problems. The most recent International Children's Continence Society (ICCS) document suggests using the term daytime lower urinary tract (LUT) conditions to group together all functional bladder problems in children [633]. As different studies have used varying definitions and criteria, it is difficult to give reliable percentages regarding the prevalence, ranging from 2–25%. In general, an age dependent trend is seen with decreasing prevalence with increasing age [634-638].

Various factors have been associated with an increased incidence of daytime LUT conditions. Risk factors for developing overactive bladder (OAB) are obesity, a history of UTIs, nocturnal enuresis, a family history of LUT conditions, age of potty training, and bowel symptoms [639, 640]. Daytime LUT conditions are more frequently encountered in children if the father was also affected during childhood [641]. The coexistence of constipation, LUT conditions and recurrent UTI is well described [642]. There is no evidence to conclude if bladder problems or bowel problems are the leading cause. The prevalence of constipation in older children varies from 5–27%, approximately 90% is functional constipation without an organic cause. In children with functional constipation the prevalence of bladder symptoms has been shown to be as high as 64% [643, 644].

A link between daytime LUT conditions and neuropsychiatric developmental disorders such as ADHD (attention deficit/ hyperactivity disorder) has also been shown. In a meta-analysis there was a strong association between ADHD and LUTD in children, with an odds ratio for ADHD amongst children with LUTD of 2.99 (95% CI: 1.13–7.88, $p < 0.001$) [645]. Patients with neuropsychiatric developmental disorders usually are more likely to have more severe BBD at presentation, a lower QoL, and higher treatment resistance compared to those without a neuropsychiatric developmental disorder [646]. Furthermore, it is important to understand that in children with neuropsychiatric developmental disorders the pharmacological treatments influence concomitant bladder dysfunction, in both positive and negative ways [647].

Disturbances of the filling phase, the voiding phase or a combination of both in varying severity can be seen in children. The conditions are divided into either OAB or dysfunctional voiding. They can, of course, coincide and one may even be causative of the other. A specific type of incontinence in children is giggle incontinence. This is a sudden and involuntary episode of urinary incontinence provoked by laughter [648]. Dysfunctional bowel emptying may also be part of the clinical problems and BBD is the term used to cover concomitant bladder and bowel disturbances [633].

*13.1.1 **Filling-phase (storage) dysfunctions***

In filling-phase dysfunctions, the detrusor can be overactive, as in OAB. Overactivity of the bladder is the most common problem, seen mostly around five to seven years of age. This may lead to disturbances characterised by urgency, frequency and at times urgency incontinence. Some children habitually postpone micturition leading to voiding postponement. Therefore, holding manoeuvres such as leg crossing and squatting can often be seen in this group. Recurrent UTIs are common and high-pressure state of the bladder can be a cause for VUR.

*13.1.2 **Voiding-phase (emptying) dysfunctions***

In voiding-phase dysfunctions, the detrusor can be underactive, as in underactive bladder. In children with an underactive detrusor, voiding occurs with reduced or minimal detrusor contractions with post-void residuals. Urinary tract infections, straining to void, constipation and incontinence is common. Incontinence often occurs when the bladder is over-distended in the form of overflow incontinence.

During the voiding-phase incomplete relaxation or tightening of the sphincteric mechanism and pelvic floor muscles results in staccato voiding pattern (continuous urine flow with periodic reductions in flow rate precipitated by bursts of pelvic floor activity) or an interrupted voiding pattern (unsustained detrusor contractions resulting in infrequent and incomplete voiding, with micturition in fractions). The general term for this condition is dysfunctional voiding and is associated with elevated bladder pressure and PVR. Symptoms will vary depending on the severity of dyscoordination between bladder and the sphincter. Staccato voiding is seen in less severe forms and interrupted voiding and straining is seen in more severe forms.

In dysfunctional voiding, high voiding pressures generated by bladder working against a functional obstruction caused by non-relaxing sphincter may induce not only UTIs but also VUR. It has been shown that LUTD is more significant for the occurrence of UTI than VUR itself [649]. In the majority of children with dysfunctional voiding the recurrent infections disappear following successful treatment, which confirms the hypothesis that dysfunctional voiding is the main factor responsible for the infections. Spontaneous resolution of VUR may also be seen after successful treatment of dysfunctional voiding.

13.2 Diagnostic evaluation

*13.2.1 **History and physical examination***

When evaluating a child with LUT conditions, a comprehensive, structured medical history should be performed. Furthermore, a voiding diary should be taken for a minimum of two days, which includes micturition frequency, voided volumes, night-time urine output, number and timing of incontinence episodes and fluid intake. History taking should also include assessment of bowel function. For evaluation of bowel function in children, the Bristol Stool Scale is an easy-to-use tool [650, 651]. Several instruments and questionnaires are available to assess LUT conditions and have shown adequate results for clinical and research use [652].

During clinical examination, genital inspection should be performed to rule out abnormalities of the genitalia or meatus, and the lumbosacral spine and lower extremities should be investigated to evaluate a possible neurological cause.

*13.2.2 **Ultrasound and urinalysis***

Using US to measure rectal diameter predicts the presence of constipation and correlates well with symptom improvement in children with BBD [653, 654]. Urinalysis and urinary culture are essential to evaluate for a UTI, since transient voiding symptoms are common in the presence of UTI. In patients with recurrent UTIs and dysfunctional voiding, the upper urinary tract needs to be evaluated as well, using US and/or voiding cystography.

*13.2.3 **Urodynamics***

Uroflowmetry with post-voiding residual (PVR) evaluates the voiding and emptying ability of the bladder. This can be combined with pelvic floor electromyography to demonstrate overactivity of the pelvic floor muscles during voiding. A flow rate which reaches its maximum quickly and levels off ('tower shape') may be indicative of OAB whereas interrupted or staccato voiding patterns may be seen in dysfunctional voiding. Plateau uroflowmetry patterns are usually seen in anatomic obstruction of flow. A single uroflowmetry test may not always be representative of the clinical situation and multiple uroflowmetry tests, when all give a similar result, are more reliable. Uroflowmetry examination should be done when there is desire to empty the bladder and the voided volume should at least be 50% of the age-expected capacity ([age in years] + 1) x 30 mL for the children. While testing the child in a clinical environment, the impact of stress and mood changes on bladder function should also be taken into account [633, 655]. Some caution is warranted while interpreting uroflowmetry patterns, since inter-rater agreement for analysing uroflow curve pattern based on the ICCS criteria are variable [656].

Sometimes, there are (minor) underlying urological or neurological problems, which can only be diagnosed using (video)-urodynamic (VUD) studies or neurological evaluation. Video-urodynamics can be considered as well for patients with therapy-resistant dysfunctional voiding who are not responding to treatment and who are being considered for invasive treatment [657-659]. If neurological disease is suspected, MRI of the lumbosacral spine and medulla can help to exclude spinal dysraphisms such as tethered cord. Video-urodynamics may also be used as an initial investigational tool in patients with suspicion of reflux. In this case reflux may be observed along with bladder dynamics. Given the invasive nature of VUD, consider adequate distraction techniques and proper education of what to expect. Video-urodynamics in children can be performed with transurethral and suprapubic catheters, depending on the clinical question, and can be performed on the same day, also after placement of the suprapubic catheter [660]. However, performing VUD under general anaesthesia is not advisable [661].

13.3 Management

The treatment of daytime LUT conditions involves a multimodal approach, which is summarised in Figure 7.

*13.3.1 **Urotherapy and specific add-on interventions***

Behavioural modification, mostly referred to as urotherapy, is a term which covers all non-pharmacological and non-surgical treatment modalities. It includes standardisation of fluid intake, bowel management; timed voiding and basic relaxed voiding education. The child and family are educated about normal bladder function and responses to urgency. Voiding regimens are instituted and UTIs and any constipation are treated. Treatment is aimed at optimising bladder emptying and inducing full relaxation of the urinary sphincter or pelvic floor prior to and during voiding [662].

Strategies to achieve these goals include [662]:

1. Information and demystification, which includes explanation about normal LUT function and how a particular child deviates from normal function.
2. Instructions about what to do about the problem:
    - Regular voiding habits, sound voiding posture, pelvic floor awareness and training to relax pelvic floor and avoiding holding manoeuvres.
    - 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.

Recurrent UTIs and constipation should also be treated and prevented during the treatment period. In case of combined BBD it is advised to treat the bowel dysfunction first as LUT conditions may disappear after successful management of bowel dysfunction [663].

Treatment efficacy can be evaluated by improvement in bladder emptying and resolution of associated symptoms. A high success rate has been described for urotherapy programmes, independent of the components of the programme. A Cochrane analysis found little evidence that can help to make evidence-based treatment decisions [664]. However, the evidence level is low as most studies of urotherapy programmes are retrospective and non-controlled.

In order to improve the outcomes of urotherapy for therapy-refractory children, specific interventions can be added, including biofeedback, physiotherapy (e.g. pelvic floor exercises), alarm therapy and specialised training programs. Although good results with these treatment modalities have been reported, the level of evidence remains low, since only a few RCTs were published [665, 666].

In a meta-analysis, urotherapy including biofeedback training was effective for reducing UTIs and improving constipation. Furthermore, several urodynamic parameters improved compared to urotherapy alone [667]. The addition of pelvic floor muscle training to biofeedback improves outcomes in children with therapy-refractory DV with response rates of 59% [668]. Specialised training programs such as voiding school or bladder and bowel training programs show effective long lasting results in up to 46% of therapy-refractory children [669, 670].

*13.3.2 **Medication***

When considering medical treatment for OAB, there are several options in the paediatric population. Anticholinergic agents are still the mainstay of medical treatment, and oxybutynin is most commonly used [671]. However, the response to anticholinergics varies and many children experience side effects such as dry mouth and constipation. Although there have been reports about the use of tolterodine, fesoterodine, trospium, propiverine, and solifenacin in children, most of them are off-label depending on age and national regulations. Given the paucity of good-quality data on safety and tolerability, these medications should be used cautiously in children with close monitoring for potential side effects [672-675]. Despite the low level of evidence for the use of anticholinergics, their use is recommended because of the large number of studies reporting a positive effect on OAB symptoms. Although α-blocking agents are used occasionally, an RCT showed no benefit [676].

In recent years, the evidence supporting the effectiveness and safety of Mirabegron has been confirmed in several studies for children with OAB; however, it is still off-label for this indication in children. These results have been summarised in a systematic review by Kim et al. [677]. Both for monotherapy as well as add-on therapy improvement in continence has been reported [678, 679]. Furthermore, starting mirabegron after symptom recurrence after previous Botulinum toxin A (BoNT-A)-injections resulted in a lower need for additional BoNT-A-injections. In a prospective RCT including patients with newly diagnosed OAB, patients were randomised for either mirabegron 50mg, solifenacin 5mg or placebo [680]. After the three months study period, the overall success rate was significantly higher in both the mirabegron and solifenacin group when compared to placebo. Furthermore, patients with mirabegron had significantly fewer side effects from treatment. These findings could support the use of mirabegron in an earlier stage for treatment of OAB. In a systematic review, including three studies with patients with OAB, it is shown that the administration of mirabegron to the paediatric population is cardiovascular safe with comparable efficacy to anticholinergic therapy [681]. Similar clinical results are reported for Vibegron, but need to be confirmed in larger studies [682, 683].

*13.3.3 **Neuromodulation***

Neuromodulation can be considered a second-line treatment after (standard) urotherapy and medical therapy have failed. Various types of neuromodulation are currently used to treat daytime LUT conditions with promising results; however, a direct comparison is difficult due to the different treatment regimens that are followed. Transcutaneous electrical nerve stimulation (TENS) has shown promising results in the treatment of OAB with improvement of symptoms and urodynamic outcomes, also when used as add-on treatment to anticholinergics [684-686]. Parasacral TENS is shown to be effective both as primary treatment or as an adjunct to standard urotherapy for daytime LUT conditions and faecal incontinence [687, 688].

Posterior Tibial Nerve Stimulation (PTNS) is a minimally invasive treatment that demonstrated improved symptoms in therapy-refractory children as well as better QoL scores. This improvement has been shown to be long lasting in patients with OAB [689-691].

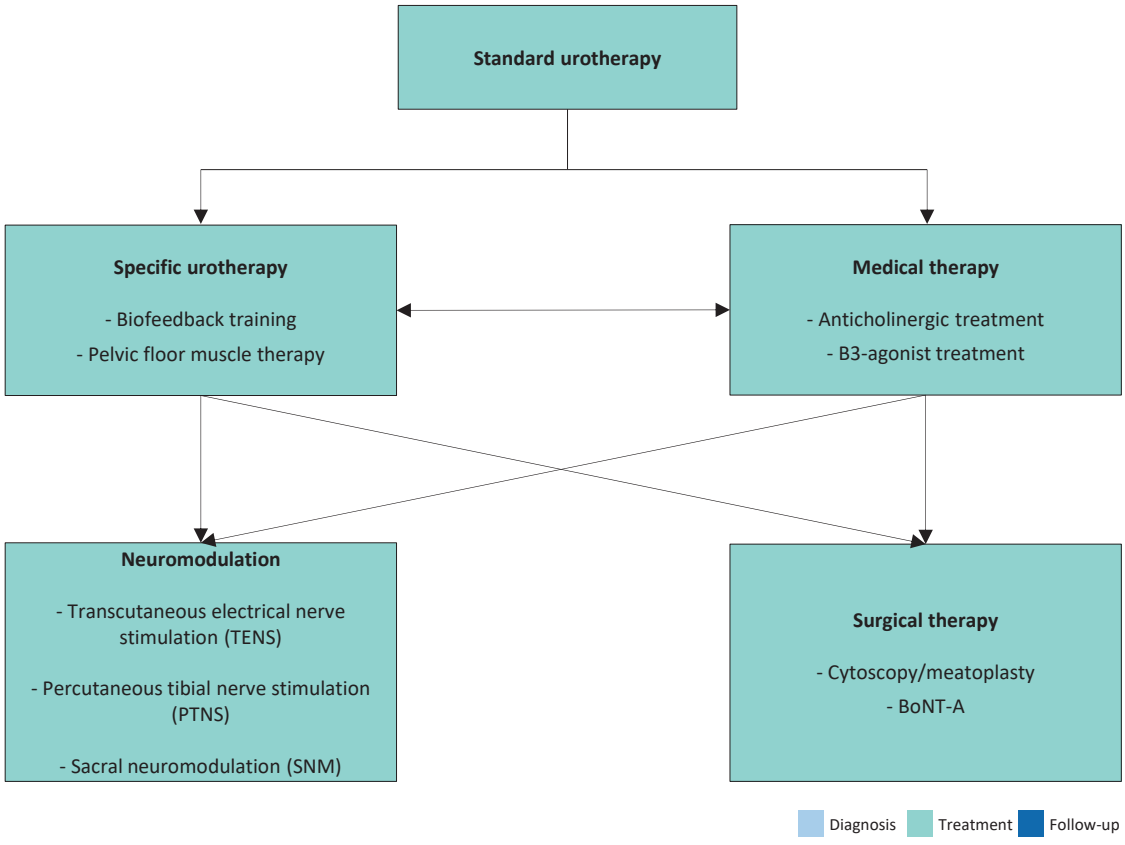
For therapy-refractory children sacral neuromodulation (SNM) has shown an improvement in symptoms of OAB; incontinence episodes, voiding frequency and QoL. This improvement is sustained in a certain group of children even after turning off the device. It is important to note that revision surgery may be necessary, especially in growing children [692].

*13.3.4 **Surgery***

In patients with LUT dysfunction, cystoscopy should be performed when there is suspicion of lower urinary tract obstruction, and the subvesical obstruction should be treated. Although meatal correction was successful in correcting the direction of the urinary stream in 93% of girls with an anterior deflected urinary stream, only 29% of patients became continent afterwards [693]. Therefore, it should not be offered as a standard of care.

Intravesical BoNT-A can be considered as a second-line treatment for OAB in children, especially for daytime incontinence, even though it is still used off-label [694]. Different dosages and type of toxin have been shown to be effective and safe. In patients with refractory non-neurogenic OAB symptoms, intravesical BoNT-A-injections are effective in enlarging bladder volume and reducing symptoms, particularly in the first six months after injection [695]. Furthermore, there are significant bladder capacity increases after second and third injections as well [696]. Intersphincteric BoNT-A shows promising results for children with therapy-refractory dysfunctional voiding, ideally in combination with urotherapy [697].

Figure 7: The treatment of daytime LUT conditions



13.4 Quality of life

Symptoms of incontinence have a negative impact on the QoL of patients and their caregivers [698]. Successful treatment of LUT conditions significantly improves QoL for patients and their caregivers [699].

13.5 Follow-up

After an initial successful response to biofeedback, 20% of the patients relapse within two years [700]. Children treated for LUT conditions are more likely to have urinary tract symptoms later in life [701, 702]. Furthermore, daytime wetting during adolescence showed a greater risk for mental health problems at the age of eighteen years [703]. Therefore, adequate transition into adult urology clinics is important when needed.

13.6 Summary of evidence and recommendations for the management of daytime lower urinary tract conditions

Summary of evidence	LE
Daytime LUT conditions have a high prevalence.	4
Daytime LUT conditions are often seen in combination with constipation.	2
A correlation between daytime LUT conditions and neuropsychiatric developmental disorders has been demonstrated and more-severe symptoms are seen in children with neuropsychiatric developmental disorders.	2
Standard urotherapy includes standardisation of fluid intake, bowel management, timed voiding and basic relaxed voiding education.	3
Anticholinergic agents are the mainstay of medical treatment for daytime LUT conditions and Mirabegron has shown to be effective as monotherapy or add-on therapy.	2
Neuromodulation shows promising results as adjunctive treatment for urinary and faecal incontinence. Types of neuromodulation include transcutaneous electrical nerve stimulation, posterior tibial nerve stimulation and sacral neuromodulation.	2
Daytime LUT conditions negatively influences the QoL of patients and caregivers and successful treatment significantly improves QoL.	2
Children affected by daytime LUT conditions have a higher risk of urinary tract symptoms later in life.	4

Recommendations	Strength rating
Use two-day voiding diaries and/or structured questionnaires for objective evaluation of symptoms, voiding, drinking habits and response to treatment.	Strong
Use a stepwise approach, starting with the least invasive treatment in managing daytime lower urinary tract (LUT) conditions in children (see Figure 7).	Strong
Provide adequate bowel management as part of the treatment if bladder bowel dysfunction is present.	Strong
Re-evaluate in case of treatment failure. This may consist of (video) urodynamics, magnetic resonance imaging of lumbosacral spine and cystoscopy.	Weak
Arrange adequate transition into adult urological care for children with persistent daytime LUT conditions in adolescence.	Strong

14. MONOSYMPTOMATIC NOCTURNAL ENURESIS - BEDWETTING

14.1 Epidemiology, aetiology and pathophysiology

Monosymptomatic nocturnal enuresis (NE), also known as bedwetting, is defined as an unvoluntary nocturnal incontinence. NE is a relatively frequent symptom in children: 5-10% at seven years of age and 1-2% in adolescents. There is also a gender difference in the incidence: two boys to one girl at any age [704]. With a spontaneous yearly resolution rate of 15% (at any age), NE is considered as a relatively benign condition [655, 705]. Seven out of 100 seven-year-old bedwetting children will continue to wet their bed into adulthood. Nocturnal enuresis is considered primary when a child has not yet had a prolonged period of being dry (six months). The term 'secondary NE' is used when a child or adult begins wetting again after having stayed dry.

The aetiology of nocturnal enuresis mainly consists of three factors: a high arousal threshold, high nighttime urine production and/or a nighttime overactive bladder. The high arousal is the conditional factor. In a recent study in children with refractory monosymptomatic nocturnal enuresis, compared with children without bedwetting problems, polysomnography and ambulatory urodynamic monitoring were performed, it was found that the children with refractory nocturnal enuresis had a smaller nighttime bladder volume, more frequent nighttime detrusor contractions and arousal problems. The findings of this study have confirmed what is known about the pathophysiology of nocturnal enuresis, although in both studies, polysomnography and ambulatory urodynamic monitoring were not performed in the normal home setting [706].

Non-monosymptomatic NE is defined as the condition of NE in association with daytime lower urinary tract symptoms (LUTS, recurrent UTIs and/or bowel dysfunction) [705, 707]. The presence of constipation has a negative association with bladder capacity [708].

Nocturnal enuresis has significant secondary stressful, emotional and social consequences for the child and their caregivers. A lower QoL has been reported for children with NE compared to controls, and NE can influence relationships with friends and family [709-713]. A study in six-year-old children with bedwetting problems has found a high level of shame, separation anxiety and fear of abandonment, and the author was also able to identify that the attitude of the parents contributes to these psychological problems [714]. Bedwetting children and their parents will often look for information and advice on social media, including YouTube channels, however, commercial companies can also influence this. The EAU therefore proposes a warrant for online professionalism standards (SoMe) [715, 716]. Correct information regarding the pathophysiology of nocturnal enuresis and treatment is therefore advised from the age of six to seven years onwards, with consideration given to mental status, family expectations, social issues and cultural background. A clear hereditary factor is observed in NE. If none of the parents or their immediate relatives has suffered from bedwetting, the child has a 15% chance of wetting their bed. If one of the parents or their immediate relatives have suffered from bedwetting, the chance of bedwetting increases to 44%, and if both parents have a positive history, the chance increases to 77%. However, from a genetic point of view, enuresis is a complex and heterogeneous disorder. Loci have been described on chromosomes 12, 13 and 22 [707]. A genome-wide association study (GWAS) in a large Danish population-based cohort has identified genome-wide significant loci in chromosome 6 and 13 that are associated with nocturnal enuresis. In addition, the GWAS identified protein coding genes associated with impaired sleep, increased nighttime urine production and bladder dysfunction, but also a significant genetic overlap between nocturnal enuresis and ADHD [717].

A high arousal threshold is the most important pathophysiological factor in the aetiology of NE: the child does not wake up when the bladder is full. Children with NE are considered deep but poor sleepers due to high arousal thresholds and frequently disturbed sleep. A systematic review confirmed the fact that sleep has a central role in NE [718]. Full-night polysomnographic recordings support this hypothesis by demonstrating the disruption of children's sleep microstructure [719]. In addition to the high arousal threshold, an imbalance is needed between night-time urine output and night-time bladder capacity [655, 705, 707]. Recently, attention has been given to the chronobiology of micturition, in which the existence of a circadian clock in kidney, brain and bladder is postulated [720]. 'Micturition-desired awakenings' is a new terminology that is suggested, and the authors of this study even found areas in the brain during functional MRI studies that could be responsible for waking up during sleep while being aware of feeling the urge to void [721].

It is unclear whether the age of start of toilet training or the prolonged use of diapers would have an influence on the incidence of nocturnal enuresis. One recent study was able to demonstrate that there is no influence - not even the age of becoming dry during the day had an influence. However, the same author performed a systematic review on the topic and found conflicting results, leaving as the hypothesis that the cultural influence may be important [722, 723]. This hypothesis is in line with the findings of a large (5,433 children) study in Portugal, stating that developmental disorders and sociodemographic factors play a role in the timing to become dry at night [724].

A high incidence of comorbidity and correlation between nocturnal urine production and sleep disordered breathing, such as obstructive sleep apnoea, has been found and investigated [725]. Symptoms such as habitual snoring, apnoeas, excessive sweating at night and mouth breathing in the patient history or by means of sleep questionnaires, such as the BEARS questionnaire [726], can lead to the detection of sleep disorders and/or adenotonsillar hypertrophy. When present, a consultation with the ENT specialist can be considered [727]. A recent meta-analysis of studies looking into the effect of adenoidectomy and/or tonsillectomy in children with nocturnal enuresis and obstructive sleep apnoea has shown that the so-called improvement of incidence of bedwetting after the surgery is low, and probably lower than expected. This emphasises the fact that adenoidectomy and/or tonsillectomy should not be advised or performed to treat the bedwetting problem [728, 729].

Obesity and ADHD are associated with a higher incidence of NE and a lower efficacy for treatment [730, 731]. The presence of allergic diseases has been recognised as a risk factor of NE and with a greater risk for more allergic episodes [732-734].

It is important to consider the child's and family's psychological status, because primary NE has been associated with psychopathology, such as attention deficit hyperactivity disorder (ADHD) and depressive

symptoms [735-737]. In children with ADHD, symptoms of NE are more severe, and it is important to inform the child and the parents about a delayed success rate and higher relapse rate compared to children without ADHD [738].

The search for a central aetiology has inspired researchers to perform functional MRI investigations. Recent functional and structural MRI studies have identified alterations in brain connectivity in children with nocturnal enuresis compared to healthy controls. Zhang *et al.* reported differences in whole-brain functional connectivity density in 68 affected children versus 57 controls [739]. Zhong *et al.,* found dysconnectivity between the salience network and default mode network in 33 children with enuresis compared to 33 controls, suggesting involvement of these networks in the pathophysiology [740]. In a related analysis, the same group observed abnormal resting-state functional connectivity of the hippocampus, proposing this region as a potential key node in brain-bladder control and cognitive processes linked to enuresis.

14.2 Diagnostic evaluation

The diagnosis is mainly obtained by history-taking. Focused questions to differentiate monosymptomatic versus non-monosymptomatic, primary versus secondary, comorbid factors, such as behavioural or psychological problems and sleep disorder breathing, should be asked. In addition, a two-day complete micturition and drinking diary, which records daytime bladder function and drinking habits, will further exclude comorbid factors such as LUTS and polydipsia [741].

Specific attention should be paid regarding bowel movements as irregular bowel movements can change the diagnosis from monosymptomatic NE to non-monosymptomatic NE. If constipation or faecal incontinence is found, which is reported in up to 20% of children with NE (37% occult constipation [742]), it should be treated simultaneously, and the family should be informed that constipation can negatively influence treatment outcomes [743-745].

The night-time urine production should be registered by weighing the nighttime diapers in the morning and adding the first morning voided volume [746]. The nighttime urine production should be recorded over a one-week period to diagnose an eventual differentiation between a high nighttime production (more than 130% of the age expected bladder capacity) versus a night-time OAB [741].

A physical examination should be performed, with special attention given to the child's back (to exclude any neurological problem), the external genitalia and surrounding skin, as well as to the condition of the clothes (wet underwear or encopresis).

Urine analysis is indicated if there is a sudden onset of bedwetting, a suspicion or history of UTIs, or inexplicable polydipsia.

A uroflowmetry and US is indicated only if there is a history of previous urethral or bladder surgery and presence of daytime urinary symptoms. For further evaluation, see Chapter 13 on daytime LUT conditions.

At present, there is no clinical indication nor use for a functional MRI (fMRI) in the diagnosis of NE.

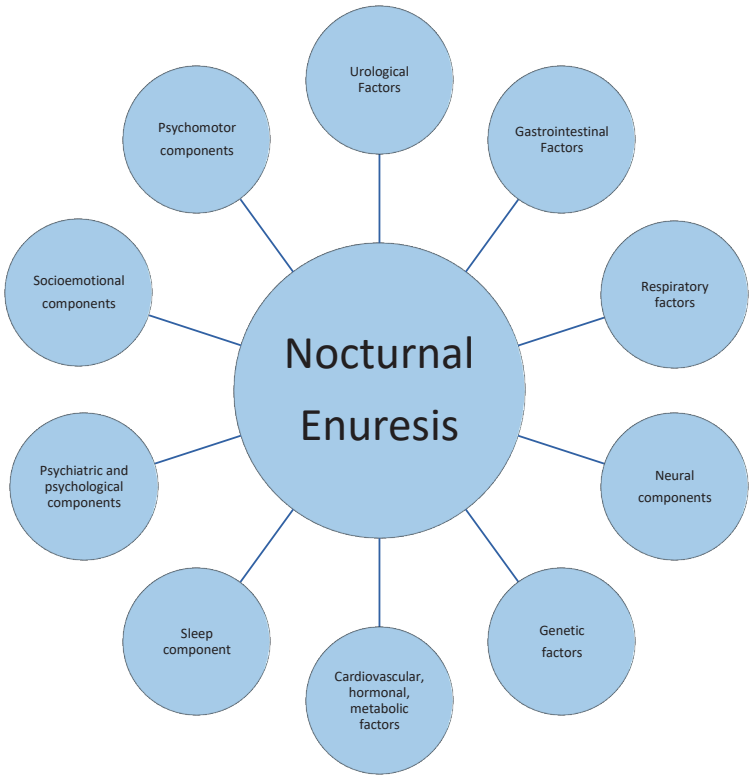
14.3 Management

As nocturnal enuresis is not an isolated phenomenon, management approaches should include a multifactorial approach. A phenotyping model suggested by Pereira *et al.* categorises NE into clinically significant phenotypic clusters. These clusters can be taken into account when developing a treatment plan [747]. Figure 8 shows the components and factors affecting nocturnal enuresis.

Before introducing any form of possible treatment, it is of utmost importance to explain the bedwetting condition to the child and the caregivers to demystify the problem. Parents should be encouraged to seek medical attention for their bedwetting children and be informed that it is known that the QoL of parents with a child with NE is negatively impaired. Medical providers assisting families with a child must be aware of this fact and guide parents by explaining that, key to treating a child with NE, is that the child is able to understand what is going on and to cooperate in the process [748].

Since the COVID-19 pandemic and the use of virtual contacts between doctors and patients, it has been shown that telemedicine is a good method of conducting close follow-up [749].

Figure 8: Components and factors contributing to nocturnal enuresis



Adapted from Pereira et al., 2024 [747].

14.3.1 ***Supportive treatment measures***

Initially, supportive measures including regular eating and drinking habits should be reviewed, stressing normal fluid intake during the day and reducing fluid intake in the hours before sleep. A reduction in caffeine intake should be encouraged [750].

Keeping a chart depicting wet and dry nights - also called basic bladder advice - has not been shown to be successful in the early treatment of NE [751]. To assure good sleep quality, specifically in children with NE, limiting the use of electronic devices before bedtime is also recommended [752].

Referral for psychological support should be advised and followed up for patients with NE and their families, particularly if the NE comorbid factor is developmental, ADHD or learning difficulties, family problems, and parental distress and possible punishment of the child are observed. Parental stress levels are higher compared to parents of non-NE children [753] and anger is found to be the most common parental reaction towards NE children [754]. This would explain why childhood traumas such as neglect and abuse are observed more often in children with NE [755]. Psychological interventions with parents of NE children were shown to significantly improve their coping mechanisms [756].

14.3.2 ***Wetting alarm treatment***

The nocturnal alarm treatment relies on the use of a device that is activated by getting wet. The goal of this therapeutic approach is that the child wakes up from the alarm - which can be acoustic or tactile - either by itself or with the help of a caregiver. By repeatedly awakening the child when wet, the method of action aims to change a high arousal to a low arousal threshold, specifically when a status of full bladder is reached. In the most recent Cochrane review (even though the quality of the included studies was low), several studies have shown that alarm treatment reduces the number of wet nights per week. An alarm treatment has a higher complete response rate and a low relapse rate compared to no treatment at all [757]. In the event of relapse after initial success, one should actively investigate for OAB [758]. The recommended length of therapy with the alarm treatment continues to be uncertain, varying from 8-12 weeks (ICCS) to 16-20 weeks [759].

Regular follow-up will improve the success. It is of utmost importance that the child play an active role in the alarm treatment and is willing to understand the purpose of the treatment modality and persevere with it.

14.3.3 ***Medical treatment***

If the child and the family would like to act on the high nighttime urine production and eventual nighttime OAB, the child should be able and willing to adjust their drinking habits and take either desmopressin or a combination of desmopressin and an anticholinergic drug.

Success rates of 70% can be obtained with desmopressin, either in tablet form (200-400µg) or as sublingual desmopressin oral lyophilisate (120-240µg). Nasal spray desmopressin is no longer recommended, due to the increased risk of overdose [760]. A rare side-effect is water intoxication, which can be prevented by adequate water intake. The dosage of 120ug has been shown to be effective and safe [761]. A structured titration increase of up to 240ug has been shown to be effective [762]. Predictive factors for success with desmopressin have been identified: older children, children with fewer wet nights, and children with high nighttime urine production [763]. Children that show a good response on low-dose desmopressin are more likely to show a complete response during the maintenance period [764]. When poor responses are seen on desmopressin, be aware of low compliance [765]. Relapse rates can be high after desmopressin discontinuation [655]. It is unclear whether structured withdrawal will result in lower relapse rates [766, 767]. In the event of desmopressin-resistant treatment for NE, or if a suspicion exists for night-time OAB, combination of desmopressin with anticholinergics is safe and efficient, even after cessation of treatment [768-771]. Recent evidence suggests increased success rates when combination therapy of two agents (desmopressin and an anticholinergic) is offered at the very beginning of the therapeutic journey [772, 773].

With nighttime OAB, a treatment failure to desmopressin can be explained because of bladder reservoir dysfunction [774]. There is no indication for monotherapy with an anticholinergic drug [775].

Newer studies suggest the use of fluoxetine as an emerging alternative [776, 777].

Alarm and desmopressin treatment have comparable efficacy in achieving > 50% reduction in wet nights. Alarms offer superior treatment response (OR: 2.89, 95% CI: 1.38-6.04) and lower relapse rates (OR: 0.25, 95% CI: 0.12-0.50) in children [778]. Multimodal treatment can achieve a partial or full response in 80% of children [779].

14.3.4 ***Electrical neuromodulation***

Several systematic reviews and randomised trials have documented potential benefits of electrical neural stimulation for NE. However, the quality of the studies included was low and different types of electrical neural stimulation, such as intra-anal stimulation and interferential current stimulation, have been included [780-783]. An RCT shows equivalent PTNS versus desmopressin effects on PMNE [784].

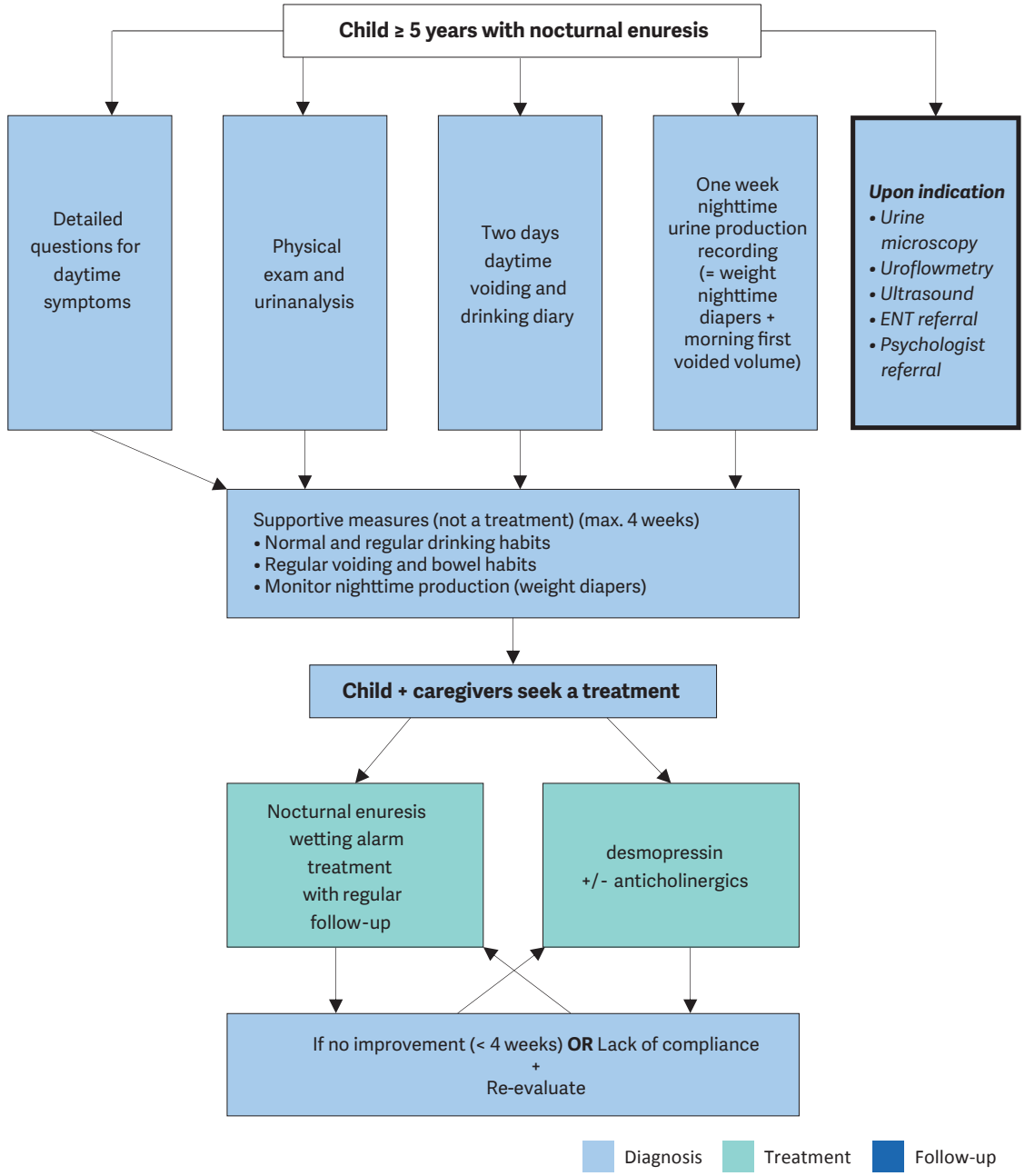
14.3.5 ***Complementary treatments:***

A Cochrane review showed no benefit for treatments such as hypnosis, psychotherapy, acupuncture, chiropractic and medicinal herbs for the treatment of NE [785]. Newer studies, however, contribute potential merit to the acupuncture practice [786, 787].

14.3.6 ***Conservative 'wait-and-see' approach***

If the child and their family are unable to comply with a treatment, if the treatment options are not possible for the family situation, and if there is no social pressure, a 'wait-and-see' approach can be chosen [788]. However, in this approach, it is important to emphasise the fact that the child should wear diapers at night to ensure a normal quality of sleep [789]. The success rate of wait and see is 15% per year, independent of age. Figure 9 presents stepwise assessment and management options for NE.

Figure 9: A stepwise assessment and management options for NE



ENT = ear, nose and throat.

14.4 Summary of evidence and recommendations for the management of monosymptomatic enuresis

Summary of evidence	LE
Chronobiology of micturition, in which the existence of a circadian clock has been proven in kidney, brain and bladder, and disturbances in this chronobiology play a major role in the pathophysiology of enuresis.	1
Aetiology of NE is multifactorial.	1

Recommendations	Strength rating
Do not treat children less than five years of age in whom spontaneous cure is likely, but rather inform the family about the involuntary nature, the high incidence of spontaneous resolution and the fact that punishment will not help to improve the condition.	Strong
Use micturition diaries or questionnaires to exclude daytime symptoms.	Strong
Perform a urine test to exclude the presence of infection or potential causes such as diabetes insipidus.	Strong
Offer supportive measures in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important.	Strong
Offer desmopressin in proven nighttime polyuria.	Strong
Offer alarm treatment in motivated and compliant families.	Strong

15. SPINAL DYSRAPHISM IN CHILDREN AND ADOLESCENTS (FORMALLY NEUROGENIC BLADDER)

In partnership with the European Reference Networks ERN eUROGEN, ERN ITHACA, ERN ERKNet, and the International Federation of Spina Bifida and Hydrocephalus (IFSBH), the Panel has developed a new joint guideline for the diagnosis and treatment of spinal dysraphism in children and adolescents. This standalone guideline has replaced the previous chapter in this guideline on neurogenic bladder in children.

This standalone guideline is available at: https://d56bochluxqnz.cloudfront.net/documents/guideline-appendices/paediatric-urology/Joint_Guidelines_on_Spinal_Dysraphism_in_children_and_-adolescents_2025.pdf

16. DILATATION OF THE UPPER URINARY TRACT (PUJ OBSTRUCTION)

16.1 Epidemiology, aetiology and pathophysiology

Dilatation of the upper urinary tract (UUT) remains a significant clinical challenge in deciding which patient will benefit from treatment. Pelviureteric junction (PUJ) 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. PUJ obstruction is the most common pathological cause of neonatal hydronephrosis [790]. PUJ obstruction appears to have a multifactorial developmental origin, with intrinsic factors such as reduced density of Cajal-like cells and differential gene expression patterns affecting hypoxia, fibrosis, inflammation and neuronal regulation, in addition to extrinsic factors [791, 792]. PUJ obstruction has an overall incidence of 1:1,500 and a ratio of males to females of 2:1 in newborns. PUJ obstruction is more common in males, and male sex is associated with a more-severe clinical course and a higher risk of reoperation compared to females [793, 794]. It is more frequent on the left side. In children with severe hydronephrosis, higher mean systolic and diastolic blood pressures may be observed compared to controls, along with elevated active renin and aldosterone concentrations, with postoperative normalisation of blood pressure following pyeloplasty but persistent elevations in renin and aldosterone levels [795].

Defining 'obstruction' can be very difficult, as there is no clear division between 'obstructed' and 'non-obstructed' urinary tracts. Currently, the most popular definition is that an obstruction represents any restriction to urinary outflow that, if left untreated, will cause progressive renal deterioration [796].

16.2 Diagnostic evaluation

The widespread use of US during pregnancy has resulted in a higher detection rate for antenatal hydronephrosis [797]. The challenge in the management of dilated UUT is to decide which child should be observed, which should be managed medically, and which requires surgical intervention. Despite the wide range of diagnostic tests, there is no single test that can accurately distinguish obstructive from nonobstructive cases (see Figure 10).

*16.2.1 **Antenatal ultrasound***

The kidneys are visualised routinely, usually between the 16th and 18th weeks of pregnancy, when almost all amniotic fluid consists of urine. The most sensitive time for foetal urinary tract evaluation is the 28th week. If dilatation is detected, US should focus on:

- laterality, severity of dilatation, and echogenicity of the kidneys;
- hydronephrosis or hydroureteronephrosis;
- bladder volume and bladder emptying;
- sex of the child; and
- amniotic fluid volume [798].

*16.2.2 **Postnatal ultrasound***

Since transitory neonatal dehydration lasts approximately 48 hours after birth, imaging should be performed following this period of postnatal oliguria. However, in severe cases (bilateral dilatation, solitary kidney, oligohydramnios), immediate postnatal sonography is recommended [799]. Renal and bladder ultrasound (RBUS) should assess the anteroposterior diameter of the renal pelvis, calyceal dilatation, kidney size, thickness of the parenchyma, cortical echogenicity, ureters, bladder wall and residual urine.

*16.2.3 **Voiding cystourethrogram***

In newborns with identified UUT dilatation, the primary or important associated factors that must be detected include:

- vesicoureteral reflux (found in up to 25% of affected children) [800];
- urethral valves;
- ureteroceles;
- diverticula; and
- neurogenic bladder.

Conventional voiding cystourethrogram (VCUG) is the method of choice for primary diagnostic procedures [801]. A VCUG is not normally considered necessary in unilateral hydronephrosis in the absence of ureteral dilatation and bladder abnormalities in RBUS performed with adequate bladder filling. VCUG should be considered in patients with urinary tract infection, ureteral dilatation or bladder abnormality, and bilateral hydronephrosis in males [802-805]. The objective in these instances is to exclude VUR, obstruction and obstructive pathologies. The routine use of VCUG prior to pyeloplasty does not impact surgical outcomes [805] and should therefore be used selectively.

*16.2.4 **Diuretic renography***

Diuretic renography is the most commonly used diagnostic tool to detect the severity and functional significance of problems with urine transport. Technetium-99m (^{99m}Tc) mercaptoacetyltriglycine (MAG3) is the radionuclide of choice. It is important to perform the study under standardised circumstances (hydration, transurethral catheter) after the fourth and sixth weeks of life [806]. Oral fluid intake is encouraged prior to the examination. At fifteen minutes before the injection of the radionuclide, it is mandatory to administer normal saline intravenous infusion at a rate of 15mL/kg over 30 minutes, with a subsequent maintenance rate of 4mL/kg/h throughout the entire period of the investigation [807]. The recommended dose of furosemide is 1mg/kg for infants during the first year of life, while 0.5mg/kg should be given to children aged one to sixteen years, up to a maximum dose of 40mg.

Beyond evaluating drainage curves, prolonged T½ drainage times have been associated with a higher likelihood of requiring surgical intervention [808]. Functional magnetic resonance urography (fMRU) is a radiation-free alternative providing detailed anatomical and functional information comparable to MAG3 renography, although its clinical use remains limited [809].

*16.2.5 **Severity classification and risk stratification***

Severity of upper urinary tract dilatation is assessed using a combination of ultrasonographic findings and functional parameters. Classification systems such as the Society for Fetal Urology (SFU) grading, anteroposterior pelvic diameter (APD) measurement, and the Urinary Tract Dilation (UTD) classification help

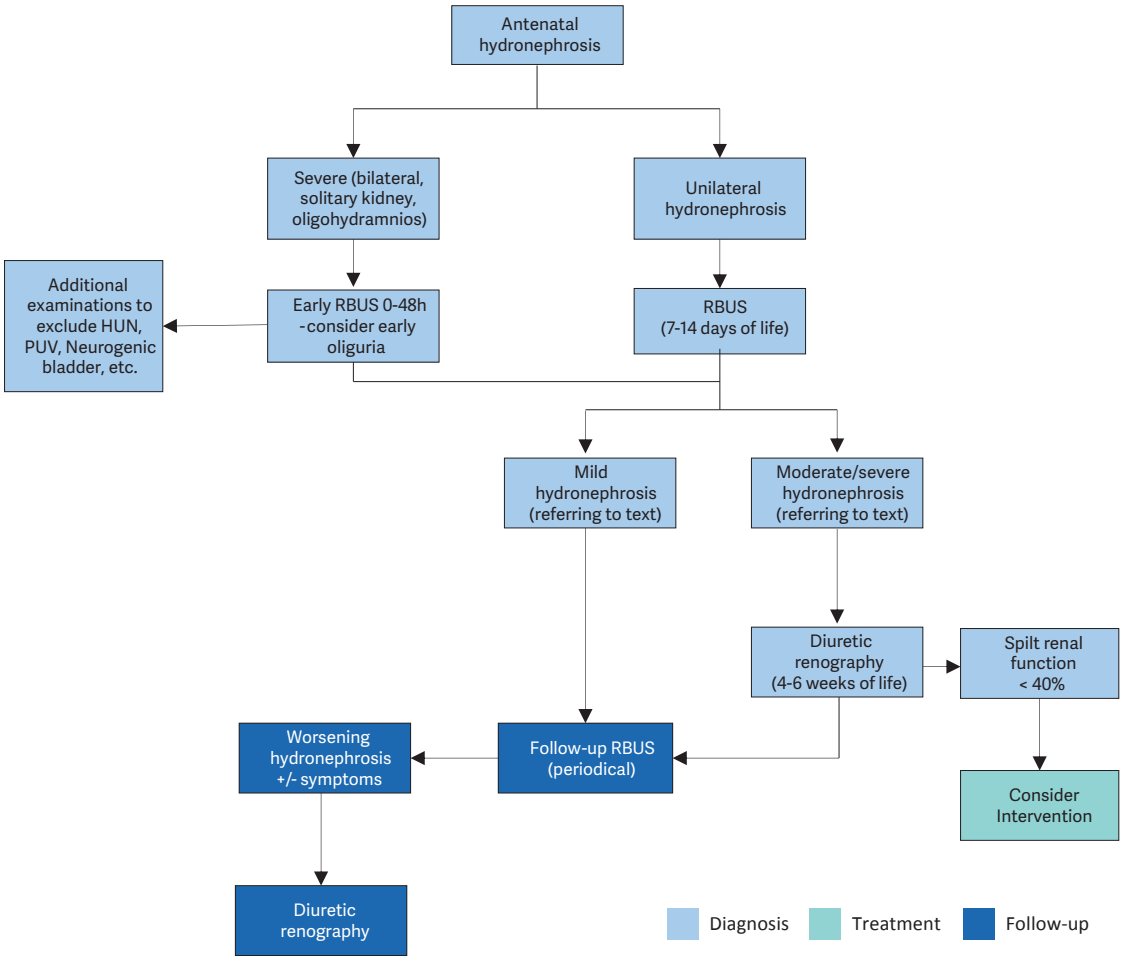
stratify risk for intervention [810-812]. No single system has been shown to be superior and universally adopted [813]. Clinical practice typically relies on integrating multiple ultrasonographic features, including calyceal dilation, parenchymal thickness, ureteral abnormalities and bladder findings, along with the assessment of drainage and renal function. Given the long-term risk of renal injury associated with UTD P2 and P3, ongoing clinical follow-up through childhood is recommended [810, 814].

16.2.6 ***Biomarkers***

Currently, urinary biomarkers may complement but cannot replace conventional imaging in the diagnostic workup of UUT dilatation. Urinary biomarkers have been evaluated as adjuncts to imaging in children with antenatal hydronephrosis and suspected obstruction. Meta-analyses and systematic reviews suggest that markers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and carbohydrate antigen 19-9 (CA19-9) may differentiate obstructive from nonobstructive dilatation and predict surgical need [815, 816]. Urinary NGAL, monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), and CA19-9 have shown associations with obstruction severity [817-820].

Combinations of markers, such as MMP-7 with TIMP-2, or biomarker panels integrated with ultrasound parameters, have further improved diagnostic accuracy [821, 822]. Although reported performance is promising, with areas under the curve of 0.80-0.90, methodological heterogeneity, limited cohort sizes, and lack of external validation preclude routine clinical application [815, 823, 824]. Moreover, these biomarkers are not universally available and not used in daily clinical practice.

Figure 10: Diagnostic algorithm for dilatation of the upper urinary tract



HUN = hydroureteronephrosis; PUV = posterior urethral valves; RBUS = renal, bladder ultrasound.

16.3 *Management*

16.3.1 Prenatal management

Counselling the caregivers of an affected child is one of the most important aspects of care. The prognosis is hopeful for a hydronephrotic kidney, even if it is severely affected, because it may still be capable of meaningful renal function, unlike a severely hypoplastic and dysplastic kidney.

16.3.1.a Continuous antibiotic prophylaxis

The benefits and harms of continuous antibiotic prophylaxis (CAP) versus observation in patients with hydronephrosis are controversial. Currently, most evidence for CAP is generally based on infants with antenatal hydronephrosis (ANH) involving various etiologies. CAP is not recommended for asymptomatic PUJ obstruction.

The Panel conducted a systematic review assessing the literature from 1980 onwards [825]. The key findings are summarised below.

Due to the heterogeneity of the published literature, no strong conclusions could be drawn as to whether CAP is superior to observation alone in children diagnosed with ANH involving various etiologies (hydronephrosis [HN], hydroureteronephrosis [HUN], vesicoureteral reflux [VUR] and so on). However, the evidence in the form of prospective and retrospective observational studies has shown that CAP reduces the risk of UTI in particular subgroups. Uncircumcised infants, HUN and high-grade HN may be more likely to develop UTI. CAP can be reserved for this subgroup of patients who are proven to be a high risk [825]. The SR was unable to identify the most effective antibiotic regime and present data on adverse effects. The most commonly chosen antibiotic in infants with ANH was trimethoprim.

16.3.2 PUJ obstruction

Management decisions must be made based on serial investigations that have used the same technique and have been performed by the same institution under standardised circumstances. Nevertheless, as the current available diagnostic tools are imprecise to some degree, indications for surgery are often amassed retrospectively and at the cost of losing irrevocably valuable renal function. According to a Cochrane review, nonsurgical management of unilateral PUJ obstruction in infants less than two years old is an option. However, the high risk of bias of the included studies limits the evidence of this systematic review [826]. In symptomatic cases (recurrent flank pain, febrile UTI), surgical correction is warranted. Additionally, surgical intervention is recommended in the event of impaired split renal function (< 40%), a decrease of split renal function of > 10% points in subsequent studies, poor drainage function after the administration of furosemide, increased anteroposterior diameter on US, and grade III and IV dilatation [827, 828] as defined by the Society for Fetal Urology [829]. Supranormal differential renal function (≥ 55%) has been observed in approximately 15% of children with suspected PUJ obstruction [830, 831]. However, current evidence suggests that supranormal function alone is not predictive of an increased need for surgical intervention [830, 831], and decisions should remain based on anatomical severity, drainage assessment and clinical symptoms.

Management of PUJ obstruction in poorly functioning kidneys (arbitrarily defined as < 20% differential function) is controversial. The chance of function improvement appears limited, so a staged approach after a trial of temporary diversion does not seem advantageous and only increase treatment burden. The options of primary pyeloplasty or nephrectomy should be discussed with the family. In addition, conservative management can be considered in some patients, but no evidence-based and shared criteria are available to date to select out these patients. Multiple parameters in addition to split function can help in the decision-making, including patient age, symptoms, degree of the dilatation, parenchymal appearance and parent preferences. While some evidence suggests that pyeloplasty may lead to improvement in DRF even in poorly functioning kidneys [832-835], interpretation is constrained by the inherent variability of DRF measurement itself, where changes may reflect methodological margin of error rather than true functional gain.

Dismembered pyeloplasty, as described by Hynes and Anderson [836], is widely recognised as the gold standard for surgical correction of PUJ obstruction, with a reported success rate of approximately 95% [822, 837-839]. Regardless of the surgical approach - open pyeloplasty (OP) or minimally invasive surgery (MIS), including laparoscopic pyeloplasty (LP) and robot-assisted laparoscopic pyeloplasty (RALP) - comparable success and complication rates have been reported [837-839]. Established advantages of MIS over OP include shorter length of hospital stays, improved cosmetic outcomes, less postoperative pain and early recovery [837, 839].

MIS in infants (≤ 1 year of age) has demonstrated comparable perioperative outcomes and similar success rates to OP, with longer operative times [822, 840].

16.4 Summary of evidence and recommendations for the management of PUJ obstruction

Summary of evidence	LE
Nowadays, most hydronephrotic kidneys have already been diagnosed prenatally during a maternal US investigation.	2
Pelviureteric junction (PUJ) obstruction is the leading pathological cause of hydronephrotic kidneys.	1
In children diagnosed with antenatal hydronephrosis, a systematic review could not establish any benefits or harms related to continuous antibiotic prophylaxis.	1b
In children diagnosed with antenatal hydronephrosis, uncircumcised infants, children diagnosed with high-grade hydronephrosis and hydroureteronephrosis were shown to be at higher risk of developing UTI.	2

Recommendations	Strength rating
Include serial ultrasound (US) and subsequent diuretic renogram and sometimes voiding cystourethrography in postnatal investigations.	Strong
Offer continuous antibiotic prophylaxis to the subgroup of children with antenatal hydronephrosis who are at high risk of developing urinary tract infection such as uncircumcised infants, children diagnosed with hydroureteronephrosis and high-grade hydronephrosis, respectively.	Weak
Decide on surgical intervention based on the time course of the hydronephrosis and the impairment of renal function.	Weak
Offer surgical intervention in case of an impaired split renal function due to obstruction or a decrease of split renal function in subsequent studies and increased anteroposterior diameter on the US, and grade IV dilatation as defined by the Society for Fetal Urology.	Weak
Offer pyeloplasty when ureteropelvic junction obstruction has been confirmed clinically or with serial imaging studies proving a substantially impaired or decrease in function.	Weak

17. VESICOURETERIC REFLUX

Lack of robust prospective RCTs limits the strength of the established guidelines for the management of VUR. The scientific literature for reflux disease is still limited and thus the level of evidence is generally low. Most of the studies are retrospective, include various patient groups and have poor stratification of quality. There is also a high risk of presenting misleading results by combining different types of studies when systematically extracting data. Therefore, for reflux disease, it is unfortunately not possible to produce recommendations based on high-quality studies.

These Guidelines aim to provide a practical approach to the treatment of VUR based on risk analysis and selective indications for both diagnostics and intervention. Although the Panel have tried to summarise most of the possible scenarios in a single table, the table itself is still quite busy. The Panel strongly share the view that making simple and practical guidelines would underestimate the complexity of VUR as a sign of a wide range of pathologies [841]. The Panel summarised and updated this chapter in a recent publication [8].

17.1 Epidemiology, aetiology and pathophysiology

Vesicoureteric reflux is an anatomical and/or functional disorder with potentially serious consequences, such as renal scarring, hypertension and renal failure. Patients with VUR present with a wide range of severity, and a good proportion of reflux patients do not develop renal scars and probably do not need any intervention [842]. Vesicoureteric reflux is a very common urological anomaly in children, with an incidence of nearly 1%.

Genetic analysis studies revealed monogenic causes for VUR and significant differentiation of innate immunity and epithelial function genes in children with VUR/UTIs compared to controls [843-845]. The main management goal is the preservation of kidney function by minimising the risk of pyelonephritis. By defining and analysing the risk factors for each patient (i.e. age, sex, reflux grade, LUTD, anatomical abnormalities and kidney status), it is possible to identify those patients with a potential risk of UTIs and renal scarring. Controversy persists

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

Many children present without symptoms of UTI and, because invasive diagnostic procedures are performed only when clinically indicated, the exact prevalence of VUR is unknown. However, the prevalence of VUR in nonsymptomatic children has been estimated at 0.4-1.8% [846]. Among infants prenatally identified with hydronephrosis on US who were screened for VUR, the prevalence was 16.2% (7-35%) [847]. Siblings of children with VUR had a 27.4% (3-51%) risk of also having VUR, whereas the offspring of parents with VUR had a higher incidence of 35.7% (21.2-61.4%) [847].

However, reflux detected by sibling screening is associated with lower grades [848] and significantly earlier resolution [849]. When VUR is discovered in siblings after UTI, it is usually high-grade and associated with a high incidence of reflux nephropathy, particularly if the sibling is male and the grade of reflux was high in the index patient [850].

The incidence of VUR is much higher among children with UTIs (30-50%, depending on age). Urinary tract infections are more common in girls than boys due to anatomical differences. However, among all children with UTIs, boys are more likely to have VUR than girls (29% vs. 14%). Boys also tend to have higher grades of VUR diagnosed at younger ages, although their VUR is more likely to resolve itself [851-854].

There is a clear coprevalence between LUTD and VUR [855]. Lower urinary tract dysfunction refers to the presence of LUTS, including urge, urge incontinence, weak stream, hesitancy, frequency and UTIs, which reflect the filling and/or emptying dysfunction and may be accompanied with bowel problems [855]. Some studies have described a prevalence of 40-60% for VUR in children with LUTD [856]. A published Swedish Reflux trial has demonstrated LUTD in 34% of patients, and subdivision into groups characteristic of children revealed that 9% had isolated overactive bladder and 24% had voiding phase dysfunction [857].

The spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical presentation and anatomy [858]. Faster resolution of VUR is more likely with age less than one 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. In several Scandinavian studies, the complete resolution rate for high-grade VUR has been reported at > 25%, which is higher than the resolution rate for VUR detected after infancy [857, 859, 860].

The presence of renal cortical abnormality, bladder dysfunction and breakthrough febrile UTIs are negative predictive factors for reflux resolution [861-863].

Dilating VUR increases the risk of developing acute pyelonephritis and renal scarring. Untreated recurrent UTIs may have a negative impact on somatic growth and medical status of the child. Evidence of renal scarring is present in 10-40% of children with symptomatic VUR, resulting from either congenital dysplasia and/or acquired post-infectious damage, which may have a negative impact on somatic growth and general well-being [864-866].

Scar rates vary among patient groups. Patients with higher grades of VUR present with higher rates of renal scars. In those with prenatal hydronephrosis, renal scarring occurs in 10% of patients [867-872], whereas in patients with LUTD, this may increase up to 30% [866, 873, 874]. Renal scarring may adversely affect renal growth and function, with bilateral scarring increasing the risk of insufficiency. Reflux nephropathy (RN) may be the most common cause of childhood hypertension. Follow-up studies have shown that 10-20% of children with RN develop hypertension or end-stage renal disease [875].

17.2 Diagnostic evaluation

The diagnostic workup should aim to evaluate the overall health and development of the child, the presence of UTIs, renal status, the presence of VUR and LUT function. A basic diagnostic workup consists of a detailed medical history (including family history and screening for LUTD), physical examination including blood pressure measurement, urinalysis (assessing proteinuria), urine culture and serum creatinine in patients with bilateral renal parenchymal abnormalities.

The standard imaging tests include renal and bladder US, VCUG and nuclear renal scans. Ultrasound and VCUG could be considered as complementary techniques [876]. The criterion standard in diagnosis of VUR is VCUG, particularly at the initial workup. This test provides precise anatomical detail and allows grading of VUR [877]. In 1985, the International Reflux Study Committee introduced a uniform system for the classification of VUR

[878, 879] (Table 2). The grading system combines two earlier classifications and is based upon the extent of retrograde filling and dilatation of the ureter, renal pelvis and calyces on VCUG [879].

Radionuclide studies for detection of reflux have lower radiation exposure than VCUG, but the anatomical details depicted are inferior [880]. Recent studies on alternative imaging modalities for detection on VUR have yielded good results with voiding US and magnetic resonance VCUG [881-884]. Contrast-enhanced voiding urosonography (ceVUS) with intravesical instillation of various ultrasound contrast agents has been shown to be highly sensitive, giving comparable results with conventional VCUG while avoiding exposure to ionising radiation [577, 885-887]. However, despite the concerns about ionising radiation and its invasive nature, conventional VCUG still remains the gold standard, because it allows better determination of the grade of VUR (in a single or duplicated kidney) and assessment of the bladder and urethral configuration. Intrarenal reflux (IRR) is associated with renal scarring development and can be diagnosed on the images acquired during the voiding phase of the standard four-staged VCUG and on ceVUS [888, 889].

Table 2: Grading system for VUR on VCUG, according to the International Reflux Study Committee [839]

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

Dimercaptosuccinic acid is the best nuclear agent for visualising the cortical tissue and differential function between both kidneys. Dimercaptosuccinic acid is taken up by proximal renal tubular cells and is a good indicator of renal parenchyma function. In areas of acute inflammation or scarring, DMSA uptake is poor and appears as cold spots. Dimercaptosuccinic acid 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 [891]. Dimercaptosuccinic acid can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis [892]. Children with a normal DMSA scan during acute UTI have a low risk of renal damage [892, 893].

Videourodynamic studies are only important in patients in whom secondary reflux is suspected, such as those with spina bifida or boys in whom VCUG is suggestive of PUV. In the case of LUTS, diagnosis and follow-up can be limited to noninvasive tests (e.g. voiding charts, US or uroflowmetry) [855]. Cystoscopy has a limited role in evaluating reflux, except for infravesical obstruction or ureteral anomalies that might influence therapy.

17.2.1 Recommendation for diagnosis of VUR

Recommendation	Strength rating
Use voiding cystourethrography for the diagnosis of vesicoureteric reflux. Contrast-enhanced voiding urosonography is another option.	Weak

17.2.2 Infants presenting with prenatally diagnosed hydronephrosis

Ultrasound of the kidney and bladder is the first standard evaluation tool for children with prenatally diagnosed hydronephrosis. The procedure is noninvasive and provides reliable information regarding kidney structure, size, parenchymal thickness and collecting system dilatation [894, 895].

Ultrasound should be delayed until the 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 about the presence of VUR. Bladder wall thickness and configuration may be an indirect sign of LUTD and reflux. The absence of hydronephrosis on postnatal US 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 one to two months of life are highly accurate for defining the presence or absence of renal pathology. In infants with two normal, successive scans, VUR is rare, and if present it is likely to be low-grade [867, 896]. 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 [847]. 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 [847]. Dimercaptosuccinic acid provides more reliable and quantitative measurement of the degree of cortical abnormalities first detected with US.

The use of VCUG is recommended in patients with US findings of bilateral high-grade hydronephrosis, duplex kidneys with hydronephrosis, ureterocele, ureteric dilatation, and abnormal bladders, because the likelihood of VUR is much higher. In all other conditions, the use of VCUG to detect reflux is optional [847, 869, 897-899].
When infants who are diagnosed with prenatal hydronephrosis become symptomatic with UTIs, further evaluation with VCUG should be considered [898]. Patients with severe hydronephrosis and those whose hydronephrosis is sustained or progressive need further evaluation to exclude obstruction.

17.2.3 Siblings and offspring of reflux patients

The screening of asymptomatic siblings and offspring is controversial. Some authors think that early identification of children with VUR may prevent episodes of UTI and therefore renal scarring, whereas others think that screening asymptomatic individuals is likely to result in significant overtreatment of clinically insignificant VUR. In screened populations, the prevalence of VUR is 27.4% in siblings and 35.7% in offspring [890]. The overall estimate for renal cortical abnormalities is 19.3% (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% (0-100%). Although early screening, and therefore early diagnosis and treatment, appears to be more effective than late screening in preventing further renal damage [847, 850, 900, 901], screening in all siblings and offspring cannot be recommended based on the available evidence. The lack of RCTs for screened patients to assess clinical health outcomes makes evidence-based guideline recommendations difficult.

17.2.4 Recommendation for paediatric screening of VUR

Recommendation	Strength rating
Inform parents of children with vesicoureteric reflux (VUR) that siblings and offspring have a high prevalence of VUR.	Strong

17.2.5 Children with febrile urinary tract infections

A routine recommendation of VCUG at zero to two years of age after the first proven febrile UTI is the safest approach, as the evidence for patient selection criteria for reflux detection is weak. Upon diagnosing a child with the first febrile UTI, the risk factors, which include age (>6 months), presence of sepsis, WBC count (≥15,000/mm), and abnormal renal US results, can be used to generate a predictive score for VUR presence [902]. (See Chapter 12 on urinary tract infections in children).

Children with febrile infections and abnormal renal US findings may have higher risk of developing renal scars and they should all be evaluated for reflux [903]. If reflux is diagnosed, further evaluation has traditionally consisted of a DMSA scan.

An alternative 'top-down' approach is also an option, as suggested by several studies in the literature. This approach involves carrying out an initial DMSA scan close to the time of a febrile UTI to determine the presence of pyelonephritis, which is then followed by VCUG if the DMSA scan reveals kidney involvement. A normal DMSA scan with no subsequent VCUG will fail to identify VUR in 5-27% of cases, with the missed VUR presumably being less significant. In contrast, a normal DMSA scan with no VCUG avoids unnecessary VCUG in >50% of those screened [573, 904-906].

17.2.6 Children with lower urinary tract symptoms and vesicoureteric reflux

Detection of LUTD is essential in treating children with VUR. It is suggested that reflux with LUTD resolves faster after LUTD correction, and that patients with LUTD are at higher risk for developing UTI and renal scarring [854, 907]. The coexistence of both conditions should be explored in any patient who has VUR. In case of symptoms suggestive of LUTD (e.g. urgency, wetting, constipation or holding manoeuvres), an extensive history and examination, including voiding charts, uroflowmetry and residual urine determination, will reliably diagnose underlying LUTD.

Among toilet-trained children, those with both LUTD and VUR are at higher risk of developing recurrent UTIs than children with isolated VUR [628]. Bladder and bowel dysfunction is common in toilet-trained children presenting with UTI with or without primary VUR. A subgroup meta-analysis also shows that functional constipation is common in these children, affecting nearly every third child. The presence of both BBD and VUR was also found to double the risk of recurrence of UTI. Therefore, all children presenting with UTI should be carefully evaluated for presence of BBD and managed accordingly [908].

In LUTD, VUR is often low-grade and US findings are normal. There is also no indication for performing VCUG in all children with LUTD, but the presence of febrile infections should be meticulously investigated. The coexistence of LUTD and VUR means it would be better to do a test covering both conditions, such as a VUDS. Any patient with LUTD and a history of febrile UTI should be investigated with a VUDS, if available. Moreover, any child who fails standard therapy for LUTD should undergo urodynamic investigation. At this stage, combining a urodynamic study with VCUG is highly recommended.

17.3 Disease management

Two main treatment approaches are available: conservative (nonsurgical) and surgical.

*17.3.1 **Nonsurgical therapy***

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

- Vesicoureteric reflux can resolve spontaneously, mostly in young patients with low-grade reflux. Renal scarring is also a significant risk factor for breakthrough UTI and could be used to determine those at risk of symptomatic VUR persistence [909].
- Resolution is nearly 80% in VUR grades I and II and 30-50% in VUR grades III-V within four to five years of follow-up.
- Spontaneous resolution is low for bilateral high-grade reflux [910].
- Vesicoureteric reflux is very unlikely to damage the kidney postnatally when patients are free of infection and have normal LUT function.
- There is no evidence that small scars, even bilateral, can cause hypertension, renal insufficiency or problems during pregnancy. Indeed, these problems during pregnancy are possible only in cases of severe bilateral renal damage.
- The conservative approach includes watchful waiting, intermittent or continuous antibiotic prophylaxis, and bladder and bowel rehabilitation in those with LUTD [873, 907, 911-913].
- Circumcision during early infancy may be considered as part of the conservative approach, because it is effective in reducing the risk of infection in normal children [914].

17.3.1.a Follow-up

Regular follow-up with imaging studies (e.g. VCUG, nuclear cystography or DMSA scan) is part of the conservative management to monitor spontaneous resolution and kidney status. Vesicoureteral reflux increases the risk of febrile UTI and renal scarring, especially when in combination with LUTD. Constipation in VUR patients with UTI is common and the prevalence can reach 27%. Assessment and management of all toilet-trained children presenting with UTI should be a part of conservative follow-up [908]. During the conservative management of high-grade infant reflux, spontaneous downgrading and resolution of VUR is more likely. However, this also depends on gender, breakthrough UTI, renal damage type and bladder dysfunction. Practical scoring systems for making decisions on further treatment, surveillance, prophylaxis or surgical intervention exist [915]. Conservative management should be dismissed in all cases of febrile breakthrough infections, despite prophylaxis, and intervention should be considered.

17.3.1.b Continuous antibiotic prophylaxis

Many prospective studies have evaluated the role of continuous antibiotic prophylaxis in the prevention of recurrent UTI and renal scarring.

Antibiotic prophylaxis may not be needed in every reflux patient [916-918]. Trials show the benefit of CAP is none or minimal in low-grade reflux. Continuous antibiotic prophylaxis is useful in patients with grades III and IV reflux in preventing recurrent infections, but its use in preventing further renal damage is not proven. For VUR children receiving CAP, younger age at the initial diagnosis of UTI (≤12 months), bilateral VUR and BBD are independent risk factors for the occurrence of breakthrough UTIs [919]. Toilet-trained children and children with LUTD derive better benefit from CAP [918, 920-924]. The RIVUR trial was the largest randomised, placebo-controlled, double-blind, multicentre study, involving 607 children aged 2-72 months with grade I-IV VUR. The RIVUR study showed that prophylaxis reduced the risk of recurrent UTI by 50%, but not renal scarring and its consequences (hypertension and renal failure), at the cost of increased antimicrobial resistance. The

benefit of prophylaxis was insignificant in patients with grade III or IV VUR and in the absence of LUTD [925-928]. Additional review of the RIVUR data based on a risk classification system defines a high-risk group (uncircumcised males, presence of BBD and high-grade reflux) who would benefit from an antibiotic prophylaxis significantly. In the context of management with CAP in VUR patients, this should be viewed as a spectrum and a shift from 'absolute' CAP in dilated VUR towards a 'selective', risk-based approach and should be supported [929]. Selecting patients who do not need CAP may be difficult and risky. A safe approach would be to use CAP in most cases. 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 sex and circumcision status. Although the 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 ensuring that there is no LUTD.

The literature generally consists of prescribing daily antibiotics at one quarter to one half the regular therapeutic dose. Trimethoprim-sulfamethoxazole, amoxicillin and nitrofurantoin are the most commonly used CAP agents. A child with a UTI and significant VUR can still be recommended to be treated conservatively at first, with surgical care reserved for incompliance for CAP, breakthrough UTIs under CAP and significant VUR that persists after long-term follow-up [919, 930].

Determination of optimal timing to discontinue CAP is controversial, however, patients administered CAP for less than a year after the last febrile UTI and those with bilateral VUR are likely to have more frequent recurrence. Administration of CAP more than one year after the last febrile UTI can potentially be beneficial to avoid recurrent UTIs [931]. Active surveillance of UTI is needed after CAP is discontinued. The follow-up scheme and the decision to perform an antireflux procedure or discontinuation of CAP should be tailored for each VUR case together with the patient and caregivers. The Panel strongly advises that the advantages and disadvantages should be discussed in detail, and easy/early access to healthcare during febrile UTIs should be taken into consideration.

One of the biggest concerns of CAP for patients, caregivers and physicians is the long-term effects of CAP. As a secondary outcome of the RIVUR study, TMP-SMZ prophylaxis for two years did not reveal any adverse effect on complete blood count (CBC), serum electrolytes and creatinine, and such routine laboratory tests in otherwise healthy children is not mandatory [932]. Impact of long-term CAP on gut microbiota in children with VUR is controversial and requires more research [933, 934].

Continuous antibiotic prophylaxis for prevention of UTIs in symptomatic VUR, which diagnosed during the workup of antenatal hydronephrosis, is recommended in the first year of life. However, the current literature remains unclear regarding whether infants diagnosed with asymptomatic VUR during the antenatal hydronephrosis workup will also benefit from CAP [935].

Recommendations	Strength rating
Treat all symptomatic patients diagnosed within the first year of life initially with continuous antibiotic prophylaxis, regardless of the grade of reflux or presence of renal scars.	Weak
Offer immediate, parenteral antibiotic treatment for febrile breakthrough infections.	Strong
Manage all children presenting at age one to five years conservatively initially.	Strong
Offer close surveillance without antibiotic prophylaxis to children presenting with lower grades of reflux and without symptoms.	Strong
Ensure that a detailed investigation for the presence of lower urinary tract dysfunction (LUTD) is performed in all children, particularly after toilet training. If LUTD is found, the initial treatment should always be for LUTD.	Strong

*17.3.2 **Surgical treatment***

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

17.3.2.a Subureteric injection of bulking materials

With the availability of biodegradable substances, endoscopic subureteric injection of bulking agents has become an alternative to long-term antibiotic prophylaxis and open surgical intervention in the treatment of VUR in children. Using cystoscopy, a bulking material is injected beneath the intramural part of the ureter in a submucosal location. The injected bulking agent elevates the ureteral orifice and supports the distal ureter and lengthens the submucosal tunnel so that coaptation is increased. This results in narrowing of the lumen, which

prevents reflux of urine into the ureter, while still allowing its antegrade flow. Reflux timing during VCUG can be used to predict the success rate of endoscopic treatment, since reflux occurring only during the voiding phase has a higher success than filling phase VUR [936].

Several bulking agents have been used over the past two decades, including polytetrafluoroethylene (PTFE or Teflon™), collagen, autologous fat, polydimethylsiloxane, silicone, chondrocytes, a solution of dextranomer/hyaluronic acid (D/HA) (Deflux™, Dexell®), and more recently polyacrylate-polyalcohol copolymer hydrogel (PPC) (Vantris®) [937, 938].

Although the best results have been obtained with PTFE [939], due to concerns about particle migration, PTFE has not been approved for use in children [940]. Although they are all biocompatible, other compounds such as collagen and chondrocytes have failed to provide a good outcome. The United States Food and Drug Administration (FDA) approved Deflux™ for the treatment of VUR in children in 2001. Injection can be performed under the ureteric orifice to create a volcanic appearance or by using a hydrodistension technique to the ureteric orifice followed by injection to the intramural ureter.

In a meta-analysis [941] of 5,527 patients and 8,101 renal units, the reflux resolution rate (by ureter) following one treatment for grades I and II reflux was 78.5%, 72% for grade III, 63% for grade IV, and 51% for grade V. 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 (73%) systems, and neuropathic (62%) versus normal (74%) bladders. The required injection volume of PPC and D/HA to achieve the same success rate can differ between agents and is generally less for PPC [942, 943].

Ureteral diameter ratio is a relatively recent objective measurement and appears to be a new predictive tool for clinical outcome and success after endoscopic injection of VUR [944].

Obstruction at UVJ (UVJO) may occur in the long-term follow-up after endoscopic correction of reflux. Patients with high-grade reflux and dilated ureters are at risk of late obstruction. Although in the short term (3-6 months) follow-up success rates and UVJ obstruction appear to be comparable in the long run, it is significantly more common when polyacrylate-polyalcohol copolymer is used as bulking substance [945-948]. The ureteral reimplantation following a failed endoscopic surgery is more challenging after PPC and distal ureter cannot be preserved and requires excision due to fibrosis [943]. Although ureteral fibrosis or inflammatory changes following Vantris injection causing UVJO has been shown to be similar to other injection materials, PPC still demonstrates a higher obstruction rate [949].

Clinical validation of the effectiveness of antireflux endoscopy is currently hampered by the lack of methodologically appropriate studies. In the most recent prospective, randomised trials comparing three treatment arms - i) endoscopic injection, ii) antibiotic prophylaxis, iii) surveillance without antibiotic prophylaxis - in 203 children aged one to two 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, after two-years follow-up. The recurrence rate at two years after endoscopic treatment was 20%. The occurrence of febrile UTIs and scar formation was highest in the surveillance group at 57% and 11%, respectively. New scar formation rate was higher with endoscopic injection (7%) compared with antibiotic prophylaxis (0%) [950]. Longer follow-up studies are needed to validate these findings.

High-grade VUR in infants can be treated with injection therapy and the resolution rate is higher than that of prophylaxis. However, this cannot be recommended for all high-grade infants with VUR, since not only are all symptomatic, but resolution or downgrading can also be achieved at favourable conditions, such as unilaterality, grade IV and low residual urine [951, 952].

17.3.2.b Open surgical techniques

Various intra- and extravesical 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%) [953].

The most popular and reliable open procedure is cross-trigonal reimplantation described by Cohen [947]. 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 technique) and infrahiatal reimplantation (Glenn-Anderson technique). If an extravesical procedure (Lich-Gregoir) is planned, cystoscopy

should be performed preoperatively to assess the bladder mucosa and the position and configuration of the ureteric orifices. In bilateral reflux, an intravesical antireflux procedure may be considered, because simultaneous bilateral extravesical reflux repair carries an increased risk of temporary postoperative urine retention [954]. Overall, all surgical procedures offer very high and similar success rates for correcting VUR.

17.3.2.c Laparoscopy and robot-assisted

There have been a considerable number of case series of transperitoneal, extravesical and pneumovesicoscopic intravesical ureteral reimplantation, which have shown the feasibility of the techniques. A recent systemic review and meta-analysis comparing laparoscopic extravesical (LEVUR) versus transvesicoscopic ureteral reimplantation (TVUR) revealed both to be good alternatives in terms of success and complication rates. Laparoscopic extravesical ureteral reimplantation is generally biasly preferred for unilateral low-grade cases and therefore appears to have a higher success and shorter hospital stay [948].

Various antireflux surgeries have been performed using the robot, and the extravesical approach is the most commonly used. Although initial reports give comparable outcomes to their open surgical counterparts in terms of successful resolution of reflux, recent meta-analysis of results of robotic-assisted laparoscopic ureteral reimplantation (RALUR) are within a wide range of variation, and on average they are poor compared to open surgery. Operative times, costs and postoperative complications leading to secondary interventions are higher with RALUR, but postoperative pain and hospital stay are less compared to open surgery [955-958].

In addition, laparoscopic or robotic-assisted approaches are more invasive than endoscopic correction and their advantages over open surgery are still debated. Therefore, at present, a laparoscopic approach cannot be recommended as a routine procedure. A laparoscopic approach can be offered as an alternative to the caregivers in centres in which there is established experience [914, 959-967]. Older children with complex anatomy and/or following a failed injection or open reimplant can specifically benefit from RALUR, since the robotic approach can facilitate the exposure. RALUR can be performed unilaterally or bilaterally, although caution is advised in bilateral cases due to the risk of transient retention [956].

De novo hydronephrosis of up to 30% can occur after extravesical RALUR and behaves similarly to open ureteral reimplantation, which is self-resolving in the overwhelming majority of cases [968].

17.4 Summary of evidence and recommendations for the management of vesicoureteric reflux in childhood

Summary of evidence
There is no evidence that correction of persistent low-grade reflux (grades I-III) without symptoms and normal kidneys offers a significant benefit.
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, because the treatment should be tailored to various risk groups.
Surgical correction should be considered in patients with persistent high-grade reflux (grades IV/V). There is no consensus on the timing and type of surgical correction. The outcome of reimplantation is better than endoscopic correction for higher grades of reflux, whereas satisfactory results can be achieved by endoscopic injection for lower grades.
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. Febrile UTI, high-grade reflux, bilaterality and cortical abnormalities are considered to be risk factors for possible renal damage. The presence of LUTD is an additional risk factor for new scars.

Recommendations	Strength rating
Offer reimplantation or endoscopic correction to patients with frequent breakthrough infections.	Weak
Offer reimplantation to patients with persistent high-grade reflux and endoscopic correction for lower grades of reflux.	Strong
Offer surgical repair to children above the age of one presenting with high-grade reflux and abnormal renal parenchyma.	Weak
Offer surgical correction if parents prefer definitive therapy to conservative management.	Strong

Select the most appropriate management option based on: • the presence of renal scars; • clinical course; • the grade of reflux; • ipsilateral renal function; • bilaterality; • bladder function; • associated anomalies of the urinary tract; • age and gender; • compliance; and • parental preference. Refer to Table 3 for risk factors and follow-up.	Weak
In high-risk patients who already have renal impairment, a more aggressive, multidisciplinary approach is needed.	Strong

Table 3: Management and follow-up according to various risk groups

Risk Groups	Presentation	Initial treatment	Comment	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 six 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	Reimplantation has better results than endoscopic surgery	Postoperative 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; VCUG = voiding cystourethrography.

18. URINARY STONE DISEASE

18.1 Epidemiology, aetiology and pathophysiology

Paediatric stone disease is an important clinical problem in paediatric urology practice. Due to its recurrent nature, every effort should be made to discover the underlying metabolic abnormality so that it can be treated appropriately. The main goal is to maintain a stone-free state with close follow-up, although it may not be possible in some circumstances (e.g. oxalosis or nephrocalcinosis).

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 [969, 970]. Hypocitraturia is the most common metabolic abnormality, followed by hypercalciuria [971]. Patients with augmented bladder constitute another important group with a risk of up to 15% [972].

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 countries. However, recent epidemiological studies have shown that the incidence of paediatric stone disease is also increasing in the Western world [973-975], particularly in girls, those with Caucasian ethnicity, African Americans and older children [976]. More than 70% of stones in children contain calcium oxalate, while infectious stones are found more frequently in younger children [977]. The risk for stone recurrence among childhood stone formers has been reported to be 35-50%. No sex differences could be found regarding the stone recurrence risk [978, 979].

18.2 Classification systems

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

*18.2.1 **Calcium stones***

Calcium stones are usually formed of calcium oxalate or calcium phosphate. Supersaturation of calcium (hypercalciuria) and oxalate (hyperoxaluria) or decreased concentration of inhibitors, such as citrate (hypocitraturia) or magnesium (hypomagnesemia), play a major role in the formation of calcium oxalate stones. Higher supersaturations of calcium oxalate were shown to be associated with multiple stone disease [980].

Hypercalciuria

This is defined by a 24-hour urinary calcium excretion of more than 4mg/kg/day (0.1mmol/kg/day) in a child weighing < 60kg. In infants younger than three months, 5mg/kg/day (0.125mmol/kg/day) is considered the upper limit for normal calcium excretion [981].

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 leading to hypercalcaemia. Urinary calcium may increase in patients with high sodium chloride intake.

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) [982].

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 [981, 982]. 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 standard criterion for the diagnosis of hypercalciuria. If calcium excretion is higher than 4mg/kg/day (0.1 mmol/kg/day), the diagnosis of hypercalciuria is confirmed and further evaluation is warranted: levels of serum bicarbonate, creatinine, alkaline phosphatase, calcium, phosphorus, magnesium, pH and parathyroid hormone. Freshly voided urine should be measured for pH [981-983]. In addition to calcium, the 24-hour urine analysis should also include phosphorus, sodium, magnesium, uric acid, citrate and oxalate.

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 accurately assess 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 [984]. A brief trial of a low-calcium diet can be carried out to determine if exogenous calcium intake and/or calcium hyperabsorption is contributing to high urinary calcium. Any recommendation to restrict calcium intake below the daily needs of the child should be avoided. Moreover, low calcium intake is a risk factor for stone formation [985] (LE: 3).

Hydrochlorothiazide and other thiazide-type diuretics may be used to treat idiopathic hypercalciuria, especially with calcium renal leak, at a starting dosage of 0.5-1mg/kg/day [986-989] (LE: 3). In long-term use of thiazide-type diuretics, a decrease in hypocalciuric effect may be seen after the third month and may cause hypokalemia, hypocitraturia, hyperuricaemia and hypomagnesaemia. Therefore, control of blood and serum values should be performed at regular intervals. Citrate therapy is also useful if citrate levels are low or if hypercalciuria persists, despite other therapies [986, 990] (LE: 4).

Hyperoxaluria

Only 10-15% of oxalate is dietary. The average child excretes less than 50mg (0.57mmol)/1.73m2/day [991-993], 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 rare primary hyperoxaluria, one of the two liver enzymes that play a role in the metabolism of oxalate may be deficient. With increased deposition of calcium oxalate in the kidneys, renal failure may ensue, resulting in deposition of calcium oxalate in other tissues (oxalosis). The diagnosis is made based upon laboratory findings of severe hyperoxaluria and clinical symptoms. The definitive diagnosis requires a liver biopsy to assay the enzyme activity. Patients with primary hyperoxaluria exhibit a substantial clinical burden such as renal stones, UTIs and pain, requiring frequent healthcare resource use [994].

As mentioned previously, other forms of hyperoxaluria may be due to hyperabsorption of oxalate in inflammatory bowel syndrome, pancreatitis and short bowel syndrome. Nevertheless, the majority of children have ‘mild’ (idiopathic) hyperoxaluria, with only mildly elevated urine oxalate levels 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. Citrate administration increases inhibitory urine activity [986, 995].

Hypocitraturia

Citrate is a urinary stone inhibitor. It acts by binding to calcium and by directly inhibiting the growth and aggregation of calcium oxalate as well as calcium phosphate crystals. Therefore, low urine citrate may be a significant cause of calcium stone disease. In adults, hypocitraturia is the excretion of urinary citrate of less than 320mg/day (1.5mmol/day). This value must be adjusted for children depending on body size [996-998].

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 [997, 999]. The urine calcium-to-citrate ratios were higher in recurrent calcium stone forming children than solitary formers [996, 1000].

The restoration of normal citrate levels is advocated to reduce stone formation, although there are few relevant studies in children. Hypocitraturia is treated by potassium citrate at a starting dose of 1mEq/kg given in two divided doses [987]. The side effects of potassium citrate are very rare and most of the time they include non-specific gastrointestinal complaints. Potassium citrate should be used with caution in hyperkalaemic and chronic renal failure conditions.

18.2.2 ***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 10mg/kg/day (0.6mmol/kg/day) is considered to be hyperuricosuria [986]. The formation of uric acid stones is mainly dependent on the presence of an acidic urinary composition. Uric acid dissociation and solubility is strongly reduced at a pH of < 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, this condition 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 nonopaque 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 6-6.5 is sufficient to prevent uric acid stones [986]. In patients who failed conservative measures with sustaining hyperuricosuria and hyperuricemia, stone recurrences or myeloproliferative diseases, allopurinol (10mg/kg) can be used. This medication may cause several drug reactions (rash, diarrhoea, eosinophilia) and should be cautiously used in chronic renal failure patients.

18.2.3 ***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 cysteine precipitation beginning at pH levels < 7.0. Other metabolic conditions, such as hypercalciuria, hypocitraturia and hyperuricosuria, may accompany cystinuria, thus leading to the formation of mixed-composition stones. Cystine stones are faintly radiopaque and may be difficult to visualise on regular radiograph studies. These stones are also hard in texture and more difficult to disintegrate using extracorporeal shockwave lithotripsy (SWL). Cystinuric patients present with larger stones at the time of diagnosis, higher new stone formation rates, and are at higher risk of surgery [1001].

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 (better above 7.5). If this treatment fails, the use of

α-mercaptopropionyl glycine or D-penicillamine may increase cystine solubility and reduce cystine levels in urine and prevent stone formation. Side effects of these drugs are mostly mild and include gastrointestinal complaints (alterations in taste and odour), fever and rash. However, they can be associated with severe side effects, such as bone marrow depression, nephrotic syndrome and epidermolysis [1002].

*18.2.4 **Infection stones (struvite stones)***

Infection-related stones constitute nearly 5% of urinary stones in children, though incidence increases over 10% in younger ages [1003] and in nonendemic regions [977, 1004]. Bacteria capable of producing urease enzyme (*Proteus, Klebsiella, Pseudomonas*) are responsible for the formation of such stones.

Urease converts urea into ammonia and bicarbonate, alkalinising 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 the 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 the formation of such stones.

18.3 Diagnostic evaluation

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 visible, occurring with or without pain - is less common in children. However, nonvisible 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 [1005, 1006].

*18.3.1 **Imaging***

Generally, US should be used as a first approach. Renal US is very effective for identifying stones in the kidney. Many radiopaque stones can be identified with a simple abdominal flat-plate examination. The most sensitive test for identifying stones in the urinary system (especially for ureteric stones) is non-contrast helical CT scanning. It is safe and rapid, with 97% sensitivity and 96% specificity [1007-1009]. Despite its high diagnostic accuracy, because of the potential radiation hazards, its use should be reserved for cases with noninformative US and/or plain abdominal radiograph. Low dose protocols have also been developed with the goal of reducing radiation dose with adequate image quality [1010]. Intravenous pyelography is rarely used in children but may be needed to delineate the caliceal anatomy prior to percutaneous or open surgery.

*18.3.2 **Metabolic evaluation***

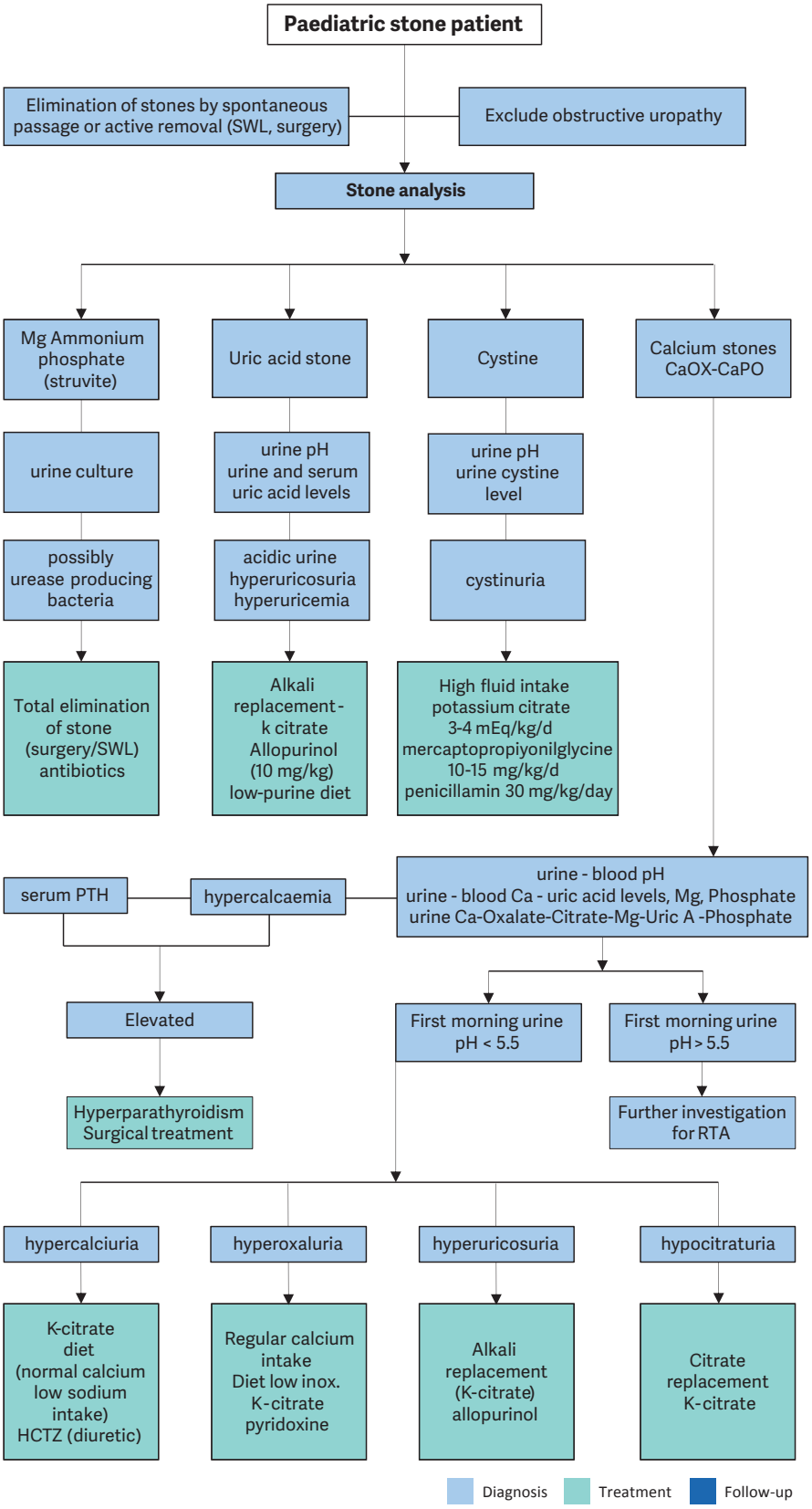
Due to the high incidence of predisposing factors for urolithiasis in children and high stone recurrence rates, every child with a urinary stone should be given a complete metabolic evaluation [969, 1002, 1011-1013]. A limited urinary metabolic evaluation (24h calcium, 24h citrate and 24h oxalate and low urinary volume) is able to detect the vast majority of clinically significant metabolic abnormalities [1014]. However, most of the time collections are inadequate and must be repeated [1015].

Metabolic evaluation includes:

- family and patient history of metabolic problems and dietary habits;
- analysis of stone composition (following stone analysis, metabolic evaluation can be modified according to the specific stone type);
- electrolytes, blood/urea/nitrogen (BUN), creatinine, calcium, phosphorus, alkaline phosphatase, uric acid, total protein, carbonate, albumin, and parathyroid hormone (if there is hypercalcaemia);
- spot urinalysis and urine culture, including ratio of calcium to creatinine;
- urine tests, including a 24-hour urine collection for calcium, phosphorus, magnesium, oxalate, uric acid citrate, protein, and creatinine clearance; and
- 24-hour cystine analysis if cystinuria is suspected (positive sodium nitroprusside test, cystine stone, cystine hexagonal crystals in urine).

Figure 11 provides an algorithm on how to perform metabolic investigations in urinary stone disease in children and how to plan medical treatment accordingly.

Figure 11: Algorithm for metabolic investigations in urinary stone disease in children



Ca = calcium; HCTZ = hydrochlorothiazide; Mg = magnesium; Ox = oxalate; PTH = parathyroid hormone; RTA = renal tubular acidosis; SWL = extracorporeal shockwave lithotripsy; Uric A = uric acid.

18.3.3 ***Urolithiasis in infants***

Approximately 9-23% of paediatric urolithiasis patients are under one year old. Infantile urolithiasis appears to be a separate entity since the aetiology and the clinical course of the disease is different than in other age groups. A study on 2,513 children with urolithiasis demonstrated that microlithiasis (< 3mm) in infants should be differentiated from other age groups since the majority of them (85%) resolve spontaneously after one year of follow-up. It has also been shown that underlying metabolic abnormality is different than in older children. In this specific age group, calcium oxalate stones are not as common as in older age groups, whereas ammonium acid urate stones are more common [970, 1016]. However, if the stone size increases or the patient becomes symptomatic during follow-up, the stones should be treated appropriately. Another study found that only 15% of infantile urolithiasis required intervention after one-year follow-up, and the only predictor for intervention was the size of the stone [1017]. Two other studies concluded that stone size larger than 4.5mm and 5mm in infants are more likely to require intervention [1018, 1019]. Therefore, observation should be the primary option for the majority of the infantile urolithiasis. If the patient becomes symptomatic or there is an increase in size, intervention can be discussed.

If an intervention is planned, SWL, retrograde intrarenal surgery (RIRS) or percutaneous nephrolithotomy (PCNL) can be offered, depending on the characteristics of the stone and the patient. All treatment modalities were found to be feasible with high success rates in infants [1020-1022].

18.4 Management

Adequate fluid intake and restricting the use of salt within daily allowance range are the general recommendations besides the specific medical treatment against the detected metabolic abnormalities. With the advance of technology, stone management has changed from open surgical approaches to endoscopic techniques that are less invasive. Deciding on the type of treatment depends on the number, size, location, stone composition and the anatomy of the urinary tract [1012, 1023, 1024]. Expectant management is the initial approach in children with asymptomatic small size stones (< 4-5mm) with a possibility of spontaneous clearance.

A study in a paediatric population showed that stone size > 6.7mm and haematuria were negative predictors for spontaneous stone passage [1025]. There is no consensus on the size of stones for different ages eligible for clearance and the duration of conservative follow-up. Adult literature reveals the benefits of medical expulsive therapy (MET) using α-blockers. Although experience in children is limited showing various results [1026], a meta-analysis of three randomised and two retrospective studies demonstrate that treatment with MET results in increased odds of spontaneous ureteral stone passage and a low rate of adverse events [1013, 1027]. Stone size and ureteral wall thickness were found to be highly predictive for MET success. Patient age, BMI, stone density and degree of hydronephrosis had no predictive value in this aspect [1028]. Another RCT in the age group of six to fourteen years comparing the effectivity of silodosin, tamsulosin and placebo as MET for distal ureteric stones less than 1cm revealed higher stone expulsion rate for Silodosin (89.3%), compared to tamsulosin (74.5%) and placebo (51.8%) in children [1029]. A Cochrane review including 125 children from one to eighteen years of age with Ca-containing idiopathic nephrolithiasis showed that oral potassium citrate may reduce recurrence after SWL. However, a substantial number of children stopped medication due to adverse events [1030].

Currently, most paediatric stones can easily be managed by SWL, RIRS or PCNL. Only a small portion of children with anatomical abnormalities may require other types of surgical intervention (open, robotic, laparoscopic). All attempts must be made to completely remove all stones since post-operative residual fragments pass spontaneously in only 20-25% of cases [1031, 1032]. A congenital obstructive uropathy should be managed together with stone removal therapy to prevent recurrence.

18.4.1 ***Extracorporeal shockwave lithotripsy***

Many reports confirm that SWL can be performed in children with no suspicion of long-term morbidity of the kidney [1033-1040].

The mean number of shockwaves for each treatment is approximately 1,800 and 2,000 (up to 4,000 if needed), and the mean power settings vary between 14kV and 21kV. Recently, two separate RCTs compared the outcomes of low versus intermediate frequency during SWL and found no significant difference [1041, 1042]. The use of US 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 [1023, 1043, 1044]. Concerns regarding anaesthesia no longer present a problem thanks to advances in technique and medication, even in the infant age group. The type of anaesthesia should be general or dissociative for children

under ten years of age, whereas conventional intravenous sedation or patient-controlled analgesia is an option for older children who are able to cooperate [1045] (LE: 2b). The general perception of paediatric SWL requiring anaesthesia has been challenged by a study showing that SWL without anaesthesia can be performed safely with comparable success rates in cooperative children >9 years of age [1046].

Stone-free rates are significantly affected by various factors. Regardless of the location, as the stone size increases, the stone-free rates decrease and retreatment rate increases. The stone-free rates for <1cm, 1-2cm, >2cm and overall, were reported as nearly 90%, 80%, 60% and 80%, respectively. As the stone size increases, the need for additional sessions increases [1023, 1043, 1044, 1047-1051]. Previous history of open surgery also decreases the success of SWL [1052].

Localisation of the calculi has been described as a significant factor affecting the success rates in various studies. Stones in the renal pelvis and upper ureter appear to respond better to SWL. For these locations, 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% [1051, 1053, 1054].

Shockwave lithotripsy can also be used to treat ureteral calculi. However, this is a more specific issue and controversial. The success rates with SWL are less for distal ureteric stones. There may also be technical problems with localisation and focusing of ureteric stones in children [1051, 1054-1056].

The type of machine used significantly influences 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, deliver less energy and have a lower risk of pulmonary trauma. However, additional treatments may be needed. The success rate is higher in younger children [1049].

Although stenting does not affect stone clearance, overall complication rates are higher and hospital stay is longer in the unstented patient with larger stones [1049, 1051]. Stenting is essential in solitary kidneys undergoing SWL 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 SWL. Post-SWL stent or nephrostomy tube placement may be needed in cases of prolonged obstruction [1002, 1048].

The Hounsfield Unit (HU) of stone on non-contrast tomography has also been shown to be a predictive factor for success in children, and SWL was found to be more successful in stones with HU of less than 600 [1032] and 1,000 [1057]. Two nomogram studies revealed male gender, younger age, smaller stone size, single stone, non-lower-pole localisation and negative history for previous intervention to be favourable factors for stone clearance in paediatric SWL [1058, 1059]. A comparative study reported that these two nomograms are independent predictors of stone-free rate following SWL in paediatric patients [1060]. A systematic review confirmed that those two nomograms have equal value in predicting outcomes of SWL in children [1061]. Although, the invention of miniaturised endoscopic instruments seems to reduce the importance and popularity of SWL, it has the advantage of not carrying the risk of certain complications related to endoscopic surgeries and with fewer postoperative emergency visits and anaesthetic sessions and less pain [1062, 1063]. Complications arising from SWL in children are usually self-limiting and transient. The most common are:

- renal colic;
- transient hydronephrosis;
- dermal ecchymosis;
- UTI;
- formation of Steinstrasse;
- sepsis; and
- hamoptysis (rare).

In children with sterile preoperative urine cultures, antibiotic prophylaxis to decrease infectious complications is not recommended [1064]. However, every effort should be made to sterilise the urine before performing SWL, ureteroscopy (URS) or PCNL.

18.4.2 ***Percutaneous nephrolithotomy***

Shockwave lithotripsy is the first choice for treating most renal paediatric stones. However, percutaneous renal surgery should be used for larger and complex stones. Preoperative evaluation, indication and surgical technique are similar in children and adults. In most cases, PCNL is used as monotherapy, 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 blood loss. However, the development of small-calibre instruments (mini PCNL, ultra-mini PCNL, super-mini PCNL and microperc) means that PCNL can be used in children. Miniaturised PCNL has several advantages compared to standard PCNL, such as a smaller skin incision, single-step dilation and sheath placement, good working access for paediatric instruments, variable length and lower cost [1064-1066].

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, SWL and URS. Even in complete staghorn cases, a clearance rate of 89% has been achieved following a single session [1067-1072]. The mean postoperative hospital stay is between one and four days and is much shorter than open surgery [1073]. The less-invasive nature of this technique has made it superior to open surgery for treating renal stones in children [1074-1081].

The most frequently reported complications of PCNL in children are bleeding, postoperative fever or infection, and persistent urinary leakage. Bleeding requiring transfusion is reported in less than 10% of patients [1077, 1080, 1082-1085] and is closely associated with stone burden, operative time, sheath size and the number of tracts [1077, 1078, 1086]. In recent studies, postoperative infectious complications, such as fever with or without documented UTI, are reported in fewer than 15% of cases [1077, 1080, 1082, 1083, 1085, 1087] and the origin of fever is not always found to be the infection. Due to the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [1067, 1088-1090].

Using high-power laser (>40W) during PCNL is feasible and may be helpful in the treatment of staghorn stones [1091], but it should be kept in mind that increased temperatures inside the smaller paediatric kidney might lead to tissue damage, as has been shown in simulation models [1092].

With the availability of smaller-size instruments, miniaturised PCNL ('minipark') through a 13F or 14F sheath [1066, 1087, 1093], as well as ultra-mini PCNL (UMP) through 12F sheaths [1094] have become possible, with decreased transfusion rates [1087]. The mini- and super-mini PCNL (SMP) were shown to have higher efficacy with low complication rates Clavien grade < 3b, which some authors deemed to be a safe alternative to SWL [1074, 1095]. In this study, 108 children under twelve years old with a single stone (10-20mm) in the renal pelvis or calyces were randomised into two groups: mini PCNL or SWL. The stone-free rate after a single session was significantly higher for PCNL (88.9%) compared to SWL (55.6%) [1074]. After second and third sessions, SWL success increased to 88.8% [1096]. The complication rates were 22.2% in PCNL and 14.8% in SWL without statistical significance.

The SMP was shown to be advantageous over mini-PCNL in terms of complications with similar stone-free rates [1096, 1097]. This miniaturisation has been further developed into the technique of 'microperc' using a 4.85F 'all-seeing needle.' This technique enables the stone to be fragmented by a laser *in situ* and left for spontaneous passage [1098]. A study revealed that microperc provides a similar SFR with similar complication rates and a lower additional treatment rate compared with SWL in the treatment of kidney stone disease in children [1099]. For stones 10-20mm, micro-PCNL was shown to have comparable results with less bleeding compared to mini-PCNL [1075] and similar outcomes with less anaesthetic sessions compared to RIRS [1081]. As experience has accumulated in adult cases, new approaches have started to be applied in children, including tubeless PCNL. This technique has been used in uncomplicated surgery for stones <2cm, with patients left either with an indwelling catheter or double-J stent in the ureter [1084, 1100] or totally tubeless [1101]. Moreover, the use of US for establishment of access is gaining popularity [1076, 1079, 1102].

Traditionally, PCNL in children is performed in prone position. Another trend in the literature is the performance of PCNL in flank-free modified supine position in children [1102, 1103]. The proposed advantages are shorter operative time and enabling a simultaneous ureteroscopic procedure without changing the position of the patient. In a recent study, 55 paediatric patients with kidney stones who underwent UMP were randomised into two groups: flank-free modified supine position versus prone position. Stone-free rates and complications rates were similar, but the operative time was found to be shorter for supine position [1104].

For postoperative pain management, two randomised controlled trials showed that intercostal nerve block or erector spinae block were shown to provide effective postoperative analgesia in paediatric patients [1105, 1106].

18.4.3 ***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. Guidewires are strongly recommended, and the procedure should be performed using direct vision. Routine balloon dilation of the ureterovesical junction and ureteral stenting are controversial. In general, ureteric dilatation is performed only in selected cases. There is a tendency to use hydrodilatation more because it is similarly effective [1067, 1107, 1108].

Various lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, have all been shown to be safe and effective. Due to the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [1109].

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. The risk of postoperative hydronephrosis depends on the presence of impacted stone and ureteral injury during operation [1110]. A multi-institutional study on the use of semirigid ureteroscopy for ureteral calculi in children showed that the procedure is effective with a 90% SFR and efficacy quotient. The study also focused on the factors affecting the complication rates. The authors found that, although operating time, age, institutional experience, orifice dilation, stenting and stone burden were significant on univariate analysis, multivariate analysis revealed that operating time was the only significant parameter affecting the complication rate [1107]. However, for proximal ureteral stones, semi-rigid ureteroscopy is not a good first option because of higher complication and failure rates [1111].

A literature review contains a growing number of case series on the use of flexible ureterorenoscopic interventions in children. Both intrarenal and ureteric stones can be treated using this approach [1112-1117]. In these series, the authors generally did not use active orifice dilation but attempted to use a ureteral sheath where possible. However, a significant problem was the inability to obtain retrograde access to the ureter in approximately half of the cases [1113, 1115]. This problem can be overcome by stenting and leaving the stent indwelling for passive dilation of the orifice and performing the procedure in a second session. The success rates varied between 60 and 100%, with a negligible number of complications [1112, 1114-1116, 1118]. The need for additional procedures was related to stone size [1116]. Radiation exposure during URS can be minimised by using Flat Panel Detector c-Arms while simultaneously improving image quality [1119].

One RCT and four other comparative studies showed that RIRS had similar stone-free rates compared to SWL after three months, with fewer sessions [1062, 1120-1123]. However, for stones larger than 20mm, RIRS monotherapy has lower stone-free rates than mini-PCNL, with the advantages of decreased radiation exposure, fewer complications and shorter hospital stay [1124]. In contrast, for stones between 10 and 20mm, RIRS has similar success and complication rates, shorter hospital stay and lower radiation exposure when compared to micro-PCNL [1125]. A recent systematic review revealed that, compared with the other two treatments, PCNL had a longer operative time, fluoroscopy time and hospital stay. Shockwave lithotripsy had a shorter hospital stay and higher retreatment rate and auxiliary rate in comparison with the other two treatments. It was also shown that PCNL presented a higher efficacy quotient than the other two treatments, and RIRS had a lower efficiency than SWL and PCNL. In the subgroup analysis of paediatric patients with stone ≤20mm, the comparative results were similar to those described above, except for the higher complication rate of PCNL than SWL [1126].

18.4.4 ***Open or laparoscopic stone surgery***

Most stones in children can be managed by SWL and endoscopic techniques. However, 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. Open surgery is also necessary in children with severe orthopaedic deformities that limit positioning for endoscopic procedures.

In centres with well-established experience, a laparoscopic approach may be a good alternative for some cases as a last resort before open surgery. Suitable candidates include patients who have a history of previously failed endoscopic procedures, complex renal anatomy (ectopic or retrorenal colon), concomitant UPJ obstruction or caliceal diverticula, megaureter or large impacted stones. Laparoscopic stone surgery by means of conventional or a robot-assisted transperitoneal or retroperitoneal approach can be attempted. However, there is limited experience with these techniques, and they are not routine therapeutic modalities [1127-1130].

Bladder stones in children can usually be managed using endoscopic techniques. A recent randomised trial compared transurethral cystolithotripsy versus percutaneous cystolithotripsy for bladder stones smaller than 30mm and found similar success and complication rates, with success rates of more than 95% [1131]. Open surgery may also be used for very large bladder stones or for bladder stones caused by an anatomical problem.

In addition to the advantages and disadvantages of each treatment modality for the specific size and location of the stone, consideration must be given to the availability of the instruments and the experience with each treatment modality before the choice of technique is made. Table 4 lists recommendations for interventional management.

Table 4: Recommendations for management in paediatric stones

Stone size and localisation*	Primary treatment option	Alternative treatment options	Comment
Infant microlithiasis (< 3mm, any location)	Observation	Intervention and/or medical treatment	Individualised decision according to size progression, symptoms and metabolic factors.
Staghorn stones	PCNL	Open/SWL	Multiple sessions and accesses with PCNL may be needed. Combination with SWL may be useful.
Pelvis < 10mm	SWL	RIRS/PCNL	
Pelvis 10-20mm	SWL/PCNL/RIRS		Multiple sessions with SWL may be needed. PCNL and RIRS have a similar recommendation grade.
Pelvis > 20mm	PCNL	SWL/RIRS	Multiple sessions with SWL may be needed.
Lower pole calyx < 10mm	Observation or SWL	PCNL/RIRS	Stone clearance after SWL is lower than other locations.
Lower pole calyx > 10mm	PCNL	RIRS/SWL	Anatomical variations are important for complete clearance after SWL.
Upper ureteric stones	SWL	URS	Flexible scopes may be needed in case of retropulsion.
Lower ureteric stones	URS	SWL	
Bladder stones	Endoscopic (transurethral or percutaneous)	SWL/Open	Open is easier and with less operative time with large stones.

** Cystine and uric acid stones excluded.*
PCNL = percutaneous nephrolithotomy; RIRS = retrograde intrarenal surgery; SWL = shockwave lithotripsy; URS = ureteroscopy.

18.5 Summary of evidence and recommendations for the management of urinary stones

Summary of evidence
The incidence of stone disease in children is increasing.
Contemporary surgical treatment is based on minimally invasive modalities. Open surgery is very rarely indicated.
The term 'clinically insignificant residual fragments' is not appropriate for children since most of them become symptomatic and require intervention.
The majority of kidney stones < 3mm in infants resolve spontaneously.

Recommendations	Strength rating
Use plain abdominal X-ray and ultrasound as the primary imaging techniques for the diagnosis and follow-up of stones.	Strong
Use low-dose, non-contrast computed tomography in cases with a doubtful diagnosis, particularly of ureteral stones or complex cases requiring surgery.	Strong
Perform a metabolic evaluation in any child with urinary stone disease. Any kind of interventional treatment should be supported with medical treatment for the underlying metabolic abnormality, if detected.	Strong
Limit open surgery under circumstances in which the child is very young with large stones, in association with congenital problems requiring surgical correction and/or with severe orthopaedic deformities that limit positioning for endoscopic procedures.	Strong
Observe infant microlithiasis unless symptoms occur or size increases significantly.	Strong

19. URETEROCELE AND ECTOPIC URETER

19.1 Ureterocele

19.1.1 Epidemiology, aetiology and pathophysiology

Ureterocele is a cystic dilatation that develops in the intravesical part of the submucosal ureter but can extend extravesically. Ureterocele is four to seven times more frequent in female than male patients; the overall incidence in autopsies is around one in 4,000 children. Approximately 80% of ureteroceles are associated with the upper moiety ureter in duplicated systems: 20% are found in single systems and 10% of ureteroceles are bilateral [1132]. The aetiology remains unclear [1133-1135]. Ureteroceles can cause obstruction of the upper moiety, but the degree of obstruction and functional impairment is variable. Histological evaluation demonstrated that the changes represent a process of maldevelopment and may not result from infections or obstruction [1136]. The presence of an ureterocele in a duplicate system increases the risk for developing a febrile UTI [1137].

19.1.2 Classification systems

Orthotopic (intravesical) ureterocele

The intravesical or orthotopic ureterocele is completely located in the bladder and is mostly associated with a single kidney system. Orthotopic ureterocele is diagnosed more frequently in older children or adults. In the orthotopic form, there is often no or only mild obstruction and the function of the moiety is normal or slightly impaired. In duplex systems, vesicoureteral reflux can be observed in 50% on the ipsilateral side and 20% on the contralateral side. Reflux into the ureterocele is uncommon [1138].

Ectopic (extravesical) ureterocele

If any portion of the ureterocele extends into the bladder neck or urethra, this is referred to as an ectopic ureterocele, which is the most common form of ureterocele (>80%). Ectopic ureterocele can be voluminous, dissociating the trigone and slipping into the urethra (caecoureterocele) and may prolapse through the urethral meatus . The ureterocele orifice is tight and located in the bladder itself or below the bladder neck. The ureter corresponding to the lower moiety is raised by the ureterocele and is frequently refluxing, but can also be compressed by the ureterocele, leading to an obstructive megaureter. A contralateral renal duplication is seen in 50% of cases. Occasionally, large ureteroceles are responsible for reflux or obstruction of the contralateral upper tract. In the ectopic ureterocele or caecoureterocele, the upper moiety is generally poorly functioning [1136].

19.1.3 Diagnostic evaluation

At present, antenatal US detects ureterocele in the majority of cases if associated with obstruction, and diagnosis is confirmed after birth by further investigations. Later in life, these anomalies can be complicated by clinical symptoms. There is a wide variation of symptoms in patients with ureterocele (from the asymptomatic patient to urosepsis, urinary retention and hydroureteronephrosis after birth).

Prenatal US easily reveals voluminous obstructive ureteroceles [1139]. In cases with a small upper moiety or a slightly obstructive ureterocele, prenatal diagnosis is difficult. Postnatally, the following clinical symptoms, besides 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 girls. In newborns, it might cause acute urinary retention.
- The early symptom of pyelonephritis in either sex may lead to the diagnosis.
- Later problems can include dysuria, recurrent cystitis, urgency, incontinence or stones.

In cases of prenatal diagnosis, at birth, US confirms the ureteral dilatation that ends at the upper moiety of a renal duplication. It also demonstrates the presence of a ureterocele in the bladder, with a dilated ureter behind the bladder. The diagnostic workup should assess the presence of bladder neck obstruction/insufficiency, vesicoureteral reflux, upper/lower moiety obstruction and upper/lower moiety function (Figure 12). VCUG is recommended for identifying ipsilateral or contralateral reflux, for assessing the bladder neck and the degree of intra-urethral prolapse of the ureterocele [1140]. However, in asymptomatic patients with an intravesical ureterocele without lower moiety dilatation, this step could possibly be omitted. Renal scintigraphy should be used to assess moiety function, which is best assessed with DMSA [1141]. Magnetic resonance urography may visualise the morphological status of the upper moiety and lower moieties and of the contralateral kidney and can detect renal scars [1142, 1143]. Using functional MR urography, differential renal function can be assessed with low intra- and interobserver variability [1144]. Urethrocystoscopy may reveal the pathology in cases where it is difficult to make the differential diagnosis between ureterocele and ectopic megaureter.

19.1.4 ***Management***

The management of an ureterocele in a duplex system is variable. When the diagnosis is made using US, prophylactic antibiotic treatment should be considered, particularly if the diameter of the distal ureter is >7mm [613]. Furthermore, management can include active surveillance, endoscopic decompression and additional surgery through an upper approach (either partial nephroureterectomy, pyeloureterostomy or high ureteroureterostomy) or lower approach (low ureteroureterostomy, ureteral reimplantation or complete primary reconstruction) [1145-1150].

In a clinically asymptomatic child with a ureterocele, management is dependent on ultrasound findings, the presence of vesicoureteral reflux and moiety function (Figure 13). In case of a nonfunctioning upper moiety, without significant obstruction of the lower moiety and without bladder outlet obstruction, initial conservative management may be undertaken, including prophylactic antibiotic treatment. Continuation of conservative management is an option in asymptomatic patients without any bladder outlet obstruction, with minimal hydroureteronephrosis of the upper moiety or low-grade (<grade III) reflux, or ureteroceles with a dysplastic moiety [1150-1152]. However, in these patients, long-term follow-up is necessary [1153]. In 58% of patients, there is spontaneous resolution or improvement of lower moiety reflux [520]. In asymptomatic patients with a decreased upper/lower moiety function, surgical treatment should be considered for nephron preservation and/or prevention of UTI.

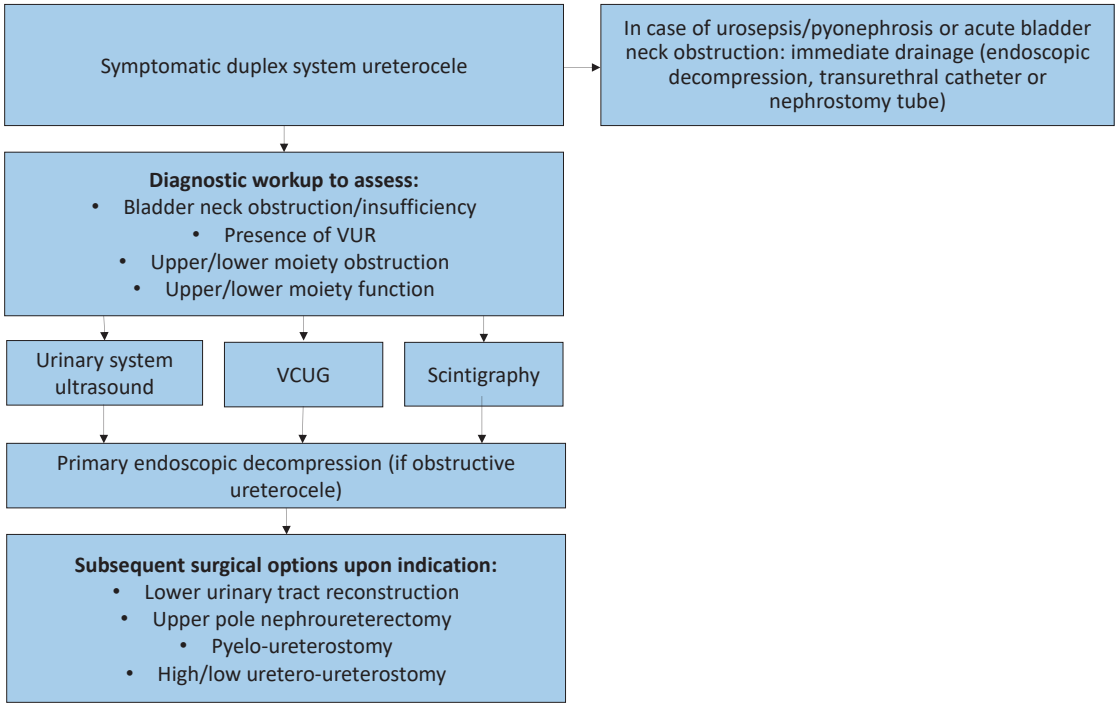
In the presence of urosepsis/pyonephrosis or obstruction at the bladder neck, immediate drainage is recommended. In severely sick children, nephrostomy drainage of the upper moiety can be considered as a first-line treatment. There are several techniques used for decompression, including cold-knife incision, electrosurgical incision and laser puncture. For orthotopic ureteroceles in particular, laser puncture shows superior results compared to electrosurgical incision with regard to secondary VUR and reoperation rate [1154]. Decompression of the dilated system facilitates later reconstructive surgery [1155, 1156]. Moreover, two systematic reviews suggest that, after primary ureterocele incision, the rate of secondary VUR and the reoperation rate is higher in those with an ectopic ureterocele and in patients with a duplex system [1157, 1158].

Additional surgery is required if primary decompression is not effective, if significant reflux is present, in case of obstruction of the ipsi- or contralateral ureters, or if there is bladder neck obstruction/insufficiency [1159]. As mentioned previously, this can be classified through an upper approach or lower approach [1149, 1160-1162]. Several single-centre case series and non-randomised comparative studies have been published regarding these various approaches with good surgical and long-term outcomes [1163-1165]. The choice of a therapeutic modality depends on the following criteria: clinical status of the patient (e.g. urosepsis); patient age; function of the upper moiety; presence of reflux or obstruction of the ipsilateral or contralateral ureter; presence of bladder neck obstruction caused by ureterocele; intravesical or ectopic ureterocele; and caregivers' and surgeon's preferences [1150, 1166]. A lower approach can be an option even in those with a poorly functioning or nonfunctioning upper moiety [1167]. The use of minimally invasive surgery, including laparoscopic, retroperitoneoscopic and robot-assisted techniques is increasing for both upper and lower approaches, with

good surgical and long-term outcomes [1168-1170]. Several studies compared the minimally invasive high ureteroureterostomy versus low ureteroureterostomy, slightly favouring the lower approach regarding operative time and severity of complications, however, these studies were nonrandomised [1171-1173].

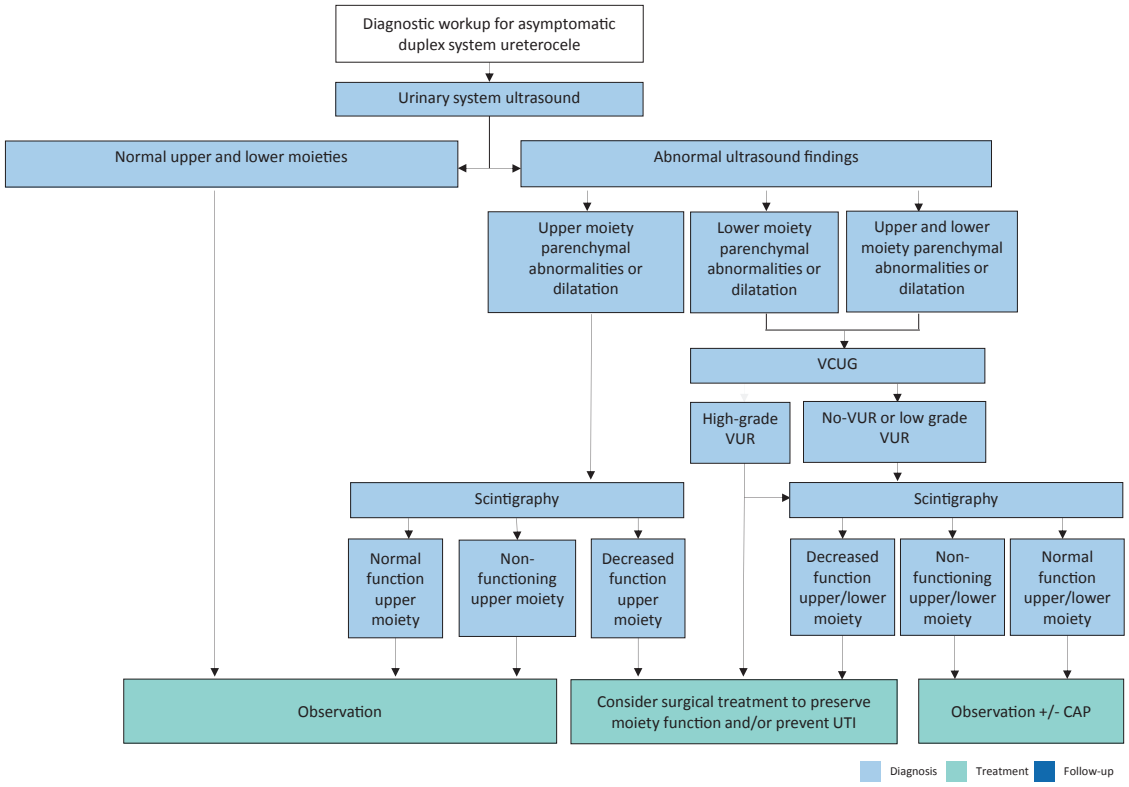
Despite favourable surgical outcomes, reconstructive surgery may not be necessary at all in some patients, as less aggressive surgical treatment and nonoperative management over time can achieve the same functional results [1174, 1175]. Long-term follow-up after surgical reconstruction is recommended, since up to 27.4% of patients can develop LUTD after lower urinary tract reconstruction, after a mean follow-up of almost 10 years [1176].

Figure 12: Diagnostic and treatment pathway for symptomatic ureterocele



VCUG = voiding cystourethrography; VUR = vesicoureteral reflux.

Figure 13: Diagnostic pathway for asymptomatic ureterocele



CAP = continuous antibiotic prophylaxis; UTI = urinary tract infection; VCUG = voiding cystourethrography; VUR = vesicoureteral reflux.

19.2 Ectopic ureter

19.2.1 Epidemiology, aetiology and pathophysiology

Ectopic ureter is less frequent than ureterocele (10 in 19,046 autopsies) and is more common in female patients as well (male to female ratio is 1:5). Some remain asymptomatic, therefore, the true incidence is difficult to determine [1177]. Eighty percent of ectopic ureters are associated with complete renal duplication. However, about 50% of ectopic ureters in male patients are associated with a single system [1178].

19.2.2 Classification

The term 'ectopic ureter' describes a ureter with the orifice located at the bladder neck, in the urethra or outside the urinary tract. The ureter can drain the upper moiety of a duplex or single system. There is a fundamental difference between the sexes. In boys, the ectopic orifice is never below the external sphincter.

In girls, the ureteral orifice may be located [1179]:

- in the urethra, from the bladder neck to the meatus (35%);
- in the vaginal vestibule (34%);
- in the vagina (25%); or
- in the uterus and fallopian tube (6%).

In boys, the ureteral orifice may be located [1179]:

- in the posterior urethra (47%);
- in the prostatic utricle (10%);
- in the seminal vesicles (33%); or
- in the vas deferens or ejaculatory ducts (10%).

19.2.3 Clinical presentation and diagnostic evaluation

Most of the ectopic ureters are diagnosed due to detection of an upper moiety ureterohydronephrosis in an asymptomatic child. In some cases, clinical symptoms can lead to diagnosis. In neonates, clinical manifestations may include pyuria and acute pyelonephritis. In young girls, persistent urinary incontinence despite normal voiding or significant vaginal discharge mimicking incontinence may be observed. In such cases, an ectopic orifice may be identified in the meatal or vaginal region [1180]. In preadolescent boys, a

specific clinical presentation may be recurrent epididymitis, and the seminal vesicle may be palpable on physical examination. Ultrasound, radionuclide studies (DMSA/MAG-3), VCUG or MRI are diagnostic tools to assess function, to detect reflux and rule out ipsilateral compression of the lower moiety and urethral obstruction [1181]. In some cases, the large ectopic ureter presses against the bladder and can look like a pseudoureterocele [1182].

*19.2.4 **Management***

In nonfunctioning moieties with recurrent infections or in girls with urinary incontinence due to continuous dribbling, surgery can be considered. Surgeries can be classified into an upper approach (partial nephroureterectomy, pyeloureterostomy or high ureteroureterostomy) or lower approach (low ureteroureterostomy, ureteral reimplantation or complete primary reconstruction). Reconstructive surgery should be considered, particularly in cases in which the upper moiety has function worth preserving. Similar to ureteroceles, all these procedures can be performed by means of an open, laparoscopic or robot-assisted approach with comparable results [1173, 1183-1186]. In patients with bilateral single ectopic ureters (a very rare condition), an individual approach is necessary, depending on the sex and renal and bladder function of the patient. Usually, the bladder neck is insufficient in these patients [1187].

19.3 Summary of evidence and recommendations for the management of obstructive pathology of renal duplication: ureterocele and ectopic ureter

Summary of evidence	LE
Ureterocele and ectopic ureter are usually associated with complete renal duplication, but they also occur in a single system.	1
Most infants are asymptomatic, while in older children, clinical symptoms will prompt assessment. The diagnosis is usually made by ultrasound.	1
The choice of surgical treatment will depend on: • clinical status of the patient (e.g. urosepsis); • patient age; • function of the upper moiety; • presence of reflux or obstruction of the ipsilateral or contralateral ureter; • presence of bladder neck obstruction caused by ureterocele; or • intravesical or ectopic ureterocele.	3
Both for ureterocele and ectopic ureter, additional surgery can be performed either through an upper approach or a lower approach.	1

Recommendations	Strength rating
Start continuous antibiotic prophylaxis (CAP) in neonates with hydroureteronephrosis due to ureterocele or ectopic ureter.	Weak
Use imaging in patients with ureterocele/ectopic ureter to assess moiety function, reflux status and obstruction.	Strong
Offer drainage such as endoscopic decompression or nephrostomy for patients with infectious obstructive ureteroceles.	Strong
Choose additional treatment based on clinical status of the patient, age, moiety function, presence of reflux or obstruction of the ipsilateral or contralateral ureter, presence of bladder neck obstruction caused by ureterocele, intravesical or ectopic ureterocele, and caregivers' and the surgeon's preferences.	Weak

20. DISORDERS/DIFFERENCES OF SEX DEVELOPMENT

20.1 Introduction

Formerly referred to as 'intersex disorders', this constellation of conditions has been the subject of a consensus document in which it was decided that the term 'intersex' should be changed to 'disorders/differences of sex development' (DSD), however, the original term is still used in the resolution of the Parliamentary Assembly of the Council of Europe (see later in this section) [1188].

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

In addition, in 2017, the Parliamentary Assembly of the Council of Europe decided on a resolution termed 'Promoting the human rights of and eliminating discrimination against intersex people' [1189]. The Assembly concluded that the majority of 'intersex' people (cited verbatim from the resolution) were physically healthy and that only a few suffered from medical conditions that put their health at risk. Furthermore, they stated that the prevailing medical view at that time was that the bodies of 'intersex' children could, and should, be made to conform to either a male or a female paradigm - often through surgical and/or hormonal intervention - and that this should be performed as early as possible so that these children could then be raised in the gender corresponding to their assigned sex. The Parliamentary Assembly considered that this approach involved serious breaches of physical integrity and autonomy, with many cases concerning very young children or infants who were unable to give informed consent and whose gender identity was unknown.

Therefore, the Parliamentary Assembly called on Council of Europe member states to effectively protect children's rights to physical integrity and bodily autonomy, and to empower 'intersex' people with the following rights: medically unnecessary *'sex-normalising'* surgery, sterilisation and other treatments practised on 'intersex' children without their informed consent should be prohibited, and additionally that it must be ensured that, except in cases in which the life of the child is at immediate risk, any treatment that seeks to alter the sex characteristics of the child, including their gonads, genitals or internal sex organs, must be deferred until such time as the child is able to participate in the decision based on the right to self-determination and on the principle of free and informed consent. The Panel refers to the above-mentioned consensus documents, as well as on the Parliamentary Assembly resolution. This chapter will focus on what is relevant for the practising paediatric urologist, as they are likely to be involved in neonates with DSD conditions.

Overall, evidence-based literature on DSD is sparse. There are no RCTs, and most studies are based on retrospective, clinical descriptive studies, or on expert opinion. An exception is made in relation to the risk of gonadal cancer, for which the level of evidence is higher [1190].

Disorders/differences of sex development can present as a prenatal diagnosis, neonatal diagnosis or late diagnosis. Prenatal diagnosis can be based on karyotype or sonographic findings; A neonatal diagnosis is based on genital ambiguity, and a late diagnosis is usually made as a result of early or delayed puberty. In these Guidelines the focus is on the neonatal presentation, where the paediatric urologist plays a more central role. Several publications have appeared over the past few decades exploring the role of prenatal corticosteroid treatment of patients with congenital adrenal hyperplasia. The Endocrine Society still proclaims their use to be restricted to research settings, and that this treatment remains experimental [1191, 1192]. For late diagnoses, we refer to endocrinology and gynaecology guidelines on precocious and delayed puberty, where paediatric urologists play a less-central role [1193, 1194].

Dealing with neonates with DSD requires a multidisciplinary approach, which should ideally include geneticists, neonatologists, paediatric and adult endocrinologists, paediatric urologists, gynaecologists, psychologists, ethicists, and social workers. Each team member should ideally be experienced in DSD, and a team should have treated enough patients to ensure experience.

A discrepancy is often perceived between research topics proposed by research scientists and those considered important by DSD patients [1195]. As a result of this discrepancy, collaborative networks such as the 'dsd-LIFE' consortium have been established to include research scientists, health professionals, patient families, and support groups (available from: https://www.dsd-life.eu/home/index.html. The focus of the DSD-LIFE study is on what patients and caregivers consider to be a priority, and research is then carried out around that issue. In addition, the newly established European Reference Network (ERN), covering rare endocrine conditions (Endo-ERN), considers patient participation in research and database management to be crucial (available from: https://endo-ern.eu/).

20.2 International consensus statements on DSD management

Four consensus statements have been published in regard to the investigations and management of DSD. In general, these statements have focused on the impact of DSD on older age groups and the importance of long-term, prospective, multidisciplinary, multicentre data collection, with a focus on patient-reported outcomes. The ultimate ambition is to preserve physical and psychological function in these future adults [1196]. The consensus proposal from the European Society of Paediatric Radiology task force focused predominantly on imaging modalities and calls for the optimisation of US in initial and interval assessments of anatomy, with MR imaging and cystovaginography used as adjunctive modalities [1197]. The COST Action BM1303 working group consensus statement from Europe raised the concern of the effects of delayed genital and gonadal surgery on physical, psychological and sexual well-being, as well as the potential malignant risks of retained gonads. Support tools need to be developed to help guide affected families and children with a balance struck between surgery and the protection of human rights [1195]. The Canadian consensus statement broadly concurs with the above but differs slightly from their European counterparts. It suggests that sex assignment need not take place at birth, and there should be a recognition of the harms caused in the past by a paucity of information to parents, and that decisions involving surgery should take place involving a shared decision model. Finally, this consensus suggests that data is insufficient to determine the correct timing of surgery [1198].

20.3 Current classification of DSD conditions

Several updates have been published since the International Consensus Conference on 'intersex' and its subsequent publications on the classification of the various conditions of DSD. The most recent of these was published by the Global DSD Update Consortium in 2016 [1199]. As the field of DSD is continuously developing, and knowledge and viewpoints change over time, an effort has been made to consider diversity, inclusion and equality, and therefore representatives from support and advocacy groups continue to be invited, with an aim of focussing on patient care and the best possible QoL.

According to the international consensus in 2005, DSDs have been defined as congenital conditions within which the development of chromosomal, gonadal and/or anatomic sex is atypical. The changes that were made according to terminology are as follows:

46XX DSD

This was formerly termed female pseudohermaphrodite, overvirilisation of an XX female, and masculinisation of an XX female. In this group, the vast majority is due to classic congenital adrenal hyperplasia (CAH) with various degrees of masculinisation. Among all DSD conditions combined, 46XX CAH patients comprise approximately 80% of cases. These conditions are extremely important because they can be potentially life-threatening days after birth due to a salt-loss phenomenon, and immediate medical care is mandatory.

46XY DSD

Previously referred to as 'male pseudohermaphroditism', undervirilisation of an XY male, and undermasculinisation of an XY male. This group is often quite heterogenous and includes the partial androgen insensitivity syndrome (PAIS), as well as the complete androgen insensitivity syndrome (CAIS) formerly referred to as 'testicular feminisation.'

Sex chromosome mosaicism DSD (45X; 45X/46XY; 47XXY)

This cohort consists of multiple variants, the most important of which being the mixed gonadal dysgenesis. Many have a normal male phenotype, and others may have asymmetric genitalia. One scrotal half often contains a gonad that is likely to be a testis, whereas the other side is more in keeping with a labia majora with usually no palpable gonad, which will most likely be a streak gonad.

Ovotesticular DSD

This was previously described as a 'true hermaphrodite' due to the presence of ovarian and testicular tissue coexisting in the same individual. There is great variability in phenotype with unilateral or bilateral undescended gonads, which can present as one ovary and one testis, or as one or two ovotestes.

Nonhormonal/nonchromosomal DSD

This cohort was recently introduced and includes newborns with cloacal exstrophy, where bladder and intestines are exposed through a midline mesenchymal defect resulting from the failure of the cloacal membrane to retract, and which then ruptures. Others in this cohort include patients with aphallia and severe micropenis. The latter is a normally formed penis with a stretched length of < 2.5 standard deviations below the mean [1188, 1200]. Micropenis should be distinguished from buried and webbed penis, which are usually of normal size. The length of the penis is measured on the dorsal aspect, while stretching the penis from the pubic symphysis to the tip of the glans [1188].

20.4 Diagnostic evaluation

20.4.1 The neonatal emergency

The first step is to recognise the possibility of DSD (Table 5) and to refer the newborn baby immediately to a tertiary paediatric centre fully equipped with neonatal, genetics, endocrinology and paediatric urology units. A diagnosis of a 46XX DSD as a result of congenital adrenal hyperplasia (the most common form of DSD) should not be delayed and represents a neonatal emergency situation due to the possibility of salt loss, which can be fatal.

Table 5: 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 nonpalpable testes in a full-term, apparently male infant
Apparent female
Clitoral hypertrophy of any degree, nonpalpable gonads
Vulva with single opening
Indeterminate
Ambiguous genitalia

20.4.2 Family history and clinical examination

A careful family history must be taken followed by a thorough clinical examination including various laboratory tests and imaging modalities (Table 6).

Table 6: Diagnostic workup of neonates with DSD

History (family, maternal, neonatal)
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
Physical examination
Pigmentation of genital and areolar area
Hypospadias or urogenital sinus
Size of phallus
Palpable and/or symmetrical gonads
Blood pressure
Investigations
Blood analysis: 17-hydroxyprogesterone, electrolytes, LH, FSH, TST, cortisol, ACTH
Urine: adrenal steroids

Genetics: karyotype, next-generation sequencing-based molecular diagnostics, WES
Ultrasound
Genitogram
hCG stimulation test to confirm presence of testicular tissue
Androgen-binding studies
Endoscopy

ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; LH = luteinising hormone; TST = testosterone; WES = whole exome sequencing.

A thorough and standardised clinical examination in a neonate presenting with ambiguous genitalia is important. In addition to an accurate description of the ambiguous genitalia, detailed information should be documented on the palpability and localisation of the gonads. Data gathered through the various examinations described below should help the team to come to a final diagnosis. Medical photography can be useful; however, this requires sensitivity and consent [1201].

Palpable gonad:
If it is possible to feel a gonad, it is most likely to be a testis. This clinical finding therefore virtually excludes 46XX DSD.

Phallus
The phallus length, phallus width and glans width 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. A single opening must be identified, as well as a hymenal ring. Attention must be given to the fusion of the labioscrotal folds, as well as to whether they show rugae or some discolouration.

Ultrasound
Can help to describe the palpated gonads or to detect nonpalpable gonads [1197]. Mullerian structures, such as the vagina or utricular structures, can be evaluated as well [1202, 1203].

Genitography
Can provide additional information on the urogenital sinus, especially on the exact position of the confluence. Moreover, genitography provides evidence of possible duplication of the vagina.

Invasive diagnostics
Can be helpful under general anaesthesia in some cases. During genitocystoscopy, the urogenital sinus, as well as the level of confluence, can be evaluated. Invasive diagnostics also allows also for evaluation of the vagina or utriculus - the possible presence of a cervix at the top of the vagina.

Laparoscopy
This is necessary to obtain a final diagnosis on the presence of impalpable gonads and on the presence of Mullerian structures. If indicated, a gonadal biopsy can be performed [1204, 1205].

Genetics
Has an increasing role in the diagnostic process of DSD. Karyotyping is usually carried out at the beginning of the diagnostic process. Although next-generation sequencing-based molecular diagnostics and whole exome sequencing (WES) are becoming the gold standard for genetic evaluation, it may be difficult to prove variant causality or relate the genotype to the clinical presentation [1206].

These investigations will help to distinguish between various conditions of DSD and provide a rapid diagnosis of congenital adrenal hyperplasia (CAH).

20.5 Gender assignment

In the current climate, it goes without saying that open, honest, and complete communication with caregivers and eventually the affected person is mandatory. Educational and psychological support regarding the impact is needed for each individual to make sense of their condition, relate to their community and establish relationships. The lack of outcome data and different preferences make it challenging to determine whether

and when to pursue gonadal or genital surgery. Shared decision-making is critical, combining expert healthcare knowledge and the right of a patient or caregivers to make fully informed decisions. This entails a process of education, sharing of risks/benefits, articulating the uncertainties in DSD care and outcomes, in addition to providing time for the patient and family to articulate back the risks and benefits of each option. The goal of all involved should be to individualise and prioritise each patient.

However, prior published 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 considered urgent. In 2017, the Parliamentary Assembly of the Council of Europe, the European Society for Paediatric Urology (ESPU), as well as the Societies for Pediatric Urology took a position in the debate on surgery for DSD [1189, 1207, 1208]. In an open letter to the Council of Europe, the European Society for Paediatric Urology expressed its attitude towards the above-mentioned resolution and concentrated on a worrying issue dealing with medicosurgical care for children with DSD. The letter stated that surgical interventions in children with DSD only being applied in emergency conditions is discordant with the definition of health according to the WHO, stating that health is not merely the absence of disease, but is a much broader concept, including physical, mental and social domains. This applies to children in particular, as favourable physical, social and emotional conditions are all critical factors for their optimal growth and development, which enables them to reach their full potential at an adult age. As social and emotional interactions with the parents or caregivers - being the most important adults in a young child's life - form the basis for their future, treatment of children with DSD can best be organised in a patient- and family-centred, multidisciplinary setting, in an atmosphere based on openness, commitment and trust. Physicians, who each day treat children with a variety of congenital conditions - as do their parents or caregivers - are committed to the current as well as the future health and well-being of all children entrusted to their care. In contrast to what is alleged in the recommendation, parents and caregivers implicitly act in the best interest of their children and should be respected as their outstanding representatives and should not be put aside by claiming prohibition regulations regarding the well-informed decisions they make on their children's behalf. Finally, in a published open letter, the ESPU advocate keeping dialogue open with the professionals active in specialised centres for multidisciplinary, patient- and family-centred care, as well as with patient societies, for which the present resolution is recognised as being a solid starting base [1209].

Genital surgery

The decision to proceed with genital surgery is acknowledged to be controversial. Patient-reported outcomes from adult patients who previously underwent early genital surgery demonstrate considerable variation, with perspectives dependent on, but not limited to, diagnostic category, gender, prior experience with surgical procedures, and contact with support groups [1210].

The majority of patients who have undergone surgery rated their appearance as satisfactory from an anatomical perspective. However, functional results were found to be less satisfactory due to the development of vaginal stenosis, or diminished sensation in the clitoris or the glans penis [1211]. Clinical decision-making with respect to genital surgery in patients with a DSD should not be made wantonly, but advisedly, in a patient and family-centred multi-disciplinary setting, on a case-by-case basis. These decisions should be supported and audited by improving information on long-term outcomes, informed consent and contact with support groups at both an individual and an institutional level.

20.6 Risk of tumour development

The dysgenetic gonads of individuals with DSD have an increased risk of developing germ cell neoplasia *in situ* (GCNIS), previously known as 'carcinoma *in situ*,' and overt germ cell cancer (GCC) as compared to the general population [1212]. The highest prevalence of GCC is seen in conditions characterised by disturbed gonadal development and in the presence of the Y chromosome or parts thereof (SRY- and GBY-encompassing regions) [1213]. In a large DSD-LIFE study, the overall prevalence of neoplastic lesions was 12%. Subanalysis demonstrated a significantly higher prevalence of 36% in patients with 46 XY gonadal dysgenesis as compared with other DSD subtypes [1214]. Conversely, patients with testosterone biosynthesis disorders and androgen action disturbances (46XY DSD group) have a much lower risk (1-15%) of GCNIS development during childhood and had a limited tendency towards invasive progression of the lesions. It has been hypothesised that a certain level of testosterone activity seems to be needed for GCNIS to progress to overt malignancy [1215, 1216]. An overview of the risks of malignancy in different subtypes of DSD is shown in Table 7.

The issue of whether gonads should be removed and the timing of such surgery remains controversial and has been altogether questioned in some forms of DSD. Patients with, for example, CAIS benefit from the presence of testicles and the resultant aromatisation of the naturally occurring testosterone to oestrogens. The risk of malignant gonadal transformation in this subcategory is low (1.5%) with cases of malignancy first appearing

after the second decade of life, thus allowing for the safe deferral of gonadectomy until after puberty [1216, 1217]. This is, however, less clear for other subtypes of DSD and needs to be assessed for each case according to several factors such as patient age, underlying DSD subtype and especially the presence of a Y chromosome. In such cases, the location of the gonad, possible fertility, hormonal potential of the gonad and the possibility of gonadal monitoring together with surgical/anaesthesic risks incurred by gonadectomy should be taken into account [1190, 1209]. In general, intra-abdominal gonads must be brought down to a superficial position or pexied to the abdominal wall to allow for monitoring, self-examination, and ultrasound-guided biopsies. High-risk gonads that fail to be brought down or streak-like gonads should be removed based on a risk- benefit analysis, and after appropriate interdisciplinary review [1190, 1209]. Biopsies should be reviewed by an experienced pathologist and specialised immunohistochemistry is recommended for measurement of expressions of placental alkaline phosphatase (PLAP) and octamer-binding transcription factors 3 and 4, as it may be difficult to differentiate between GCNIS and delayed germ cell maturation in infants. Noninvasive markers such as serum microRNA (miRNA) for early-stage malignancy detection have been developed but have yet to be implemented in clinical practice [1190, 1206].

Table 7: Risk of malignancy in various subtypes of DSD (Adapted from Looijenga *et al.*, [1218])

Risk	DSD	Malignancy risk (%)
High	Gonadal dysgenesis with Y, abdominal gonad PAIS nonscrotal gonad Frasier syndrome Denys-Drash with Y	15-35 50 60 40
Intermediate	Turner syndrome with Y 17β-hydroxysteroid dehydrogenase deficiency Gonadal dysgenesis with Y PAIS scrotal gonad	12 28 Unknown Unknown
Low	Complete androgen insensitivity syndrome Ovotesticular DSD Turner syndrome without Y	2 3 1
No	5-Alpha Reductase Deficiency Leydig cell hyperplasia	0 0

PAIS = partial androgen insensitivity syndrome.

20.7 Quality of life

In general, adult patients with DSD report good QoL and physical health. However, there is an increased risk for both somatic and psychiatric morbidities [1219]. Moreover, a lower QoL was reported in the domain 'social relationships', which relates to personal relationships and sexual health [1220, 1221]. In addition, patients with DSD report higher levels of psychological distress and mental health problems [1222, 1223]. These elements should be included in the multidisciplinary and holistic health care for these patients.

A person's experienced gender is a fundamental aspect of one's sense of self. Gender incongruence can occur when there is incongruence between the physical and experienced gender and, if this causes significant distress, fulfils the criteria for the diagnosis gender dysphoria, according to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)* of the American Psychiatric Association [1224]. Gender dysphoria is reported low in women with CAH, CAIS and complete gonadal dysgenesis favouring female sex of rearing. Gender dysphoria is reported high in females with 5α-reductase deficiency and 17β-Hydroxysteroid dehydrogenase-3 deficiency. Gender dysphoria is reported variable in PAIS or mixed gonadal dysgenesis [1225]. Approximately 3% of DSD patients undergo a gender change after puberty, which is a small group, but larger when compared to the general population [1226, 1227].

20.8 Recommendations for the management of disorders/differences of sex development

Recommendations	Strength rating
Do not delay diagnosis and treatment of any neonate presenting with ambiguous genitalia since salt loss in a 46XX CAH girl can be fatal.	Strong

Refer children to experienced centres where neonatology, endocrinology, (paediatric) urology, psychology, and transition to adult care are guaranteed.	Strong
Utilise a multidisciplinary approach and a shared decision model in patients with disorders/differences of sex development (DSD) conditions, including: a. Gender assignment; b. Genital surgery (in accordance with national regulations); and c. Gonadectomy.	Strong
Do not underestimate the significant effects on psychological and psychiatric health, quality of life, personal relationships, and sexual function in individuals with DSD.	Strong
Ensure full disclosure to patients and caregivers that the presence of a Y-chromosome in dysgenetic gonads results in a higher malignancy risk.	Strong

21. CONGENITAL LOWER URINARY TRACT OBSTRUCTION

Introduction

The term congenital lower urinary tract obstruction (CLUTO) is used to refer to intrauterine dilatation of the bladder and/or the upper urinary tract. During pregnancy, the diagnosis is usually based on ultrasound examinations. There is a broad spectrum of conditions that could cause an intrauterine dilatation of the urinary tract. Congenital lower urinary tract obstruction is most commonly the result of posterior urethral valves (PUV) in approximately 60% of cases. Postpartum diagnosis, however, comprises any number of anatomical and functional disorders/anomalies/malformations causing dilatation, e.g. anterior urethral valves, urethral atresia/stenosis, prune belly syndrome, dilating VUR, cloacal malformation, prolapsing ureterocele, megacystis-microcolon-intestinal hypoperistalsis or megacystis-megaureter syndrome [1228].

Due to the heterogeneity and the rare spectrum of clinical manifestations of CLUTO, referral of such cases is recommended to a tertiary centre with multidisciplinary expertise in prenatal and postnatal management of obstructive uropathies [1228].

Megacystis

In the first trimester, foetal megacystis is defined as a bladder with a longitudinal diameter ≥7mm. A longitudinal (craniocaudal) diameter of 7-12mm in the first trimester is usually transient, disappearing in approximately 90% of cases during the second trimester. A measurement >15mm, however, indicates that CLUTO is unlikely to resolve [1228]. In the second and third trimester, megacystis is defined by an enlarged bladder failing to empty during an extended US examination lasting at least 40 minutes. Two-thirds of cases are secondary to CLUTO, and the remainder are associated with genetic syndromes, developmental or chromosomal abnormalities, including anorectal malformations, of which 14% were normal or had an isolated urological abnormality (e.g. VUR, duplex system) [1228, 1229]. In a systematic review, ≥45% of megacystis cases were shown to be associated with oligohydramnios and 15% had chromosomal abnormalities [1230]. Final diagnoses included PUV (57%), urethral atresia/stenosis (7%), prune belly syndrome (4%), megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) (1%), cloacal abnormality (0.7%), and undefined pathologies (36.5%) [1230].

The prognosis of the foetus depends on the underlying pathology, the timing of diagnosis, the presence of oligo/anhydramnios, and bladder volume.

Posterior urethral valves

21.1 Epidemiology and pathophysiology

Posterior urethral valves are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period. The risk for chronic kidney disease (CKD) is estimated to reach 32% and 20% for end-stage renal disease (ESRD), as reported in a systemic review [1231]. Up to 17% of paediatric ESRD can be attributed to PUV [1232]. An incidence of PUV of 1 in 7,000-8,000 live births has been estimated [1233, 1234].

The kidneys start to produce urine at approximately the tenth week of antenatal life. The intrauterine obstruction leads to a decreased urine output, which could result in oligo- or anhydramnios. Amniotic fluid is necessary for normal development of the lungs, and its absence may lead to pulmonary hypoplasia.

An obstruction at the level of the urethra affects the entire urinary tract to 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 may occasionally have multiple diverticula.
- Nearly all valve patients have dilatation of the upper urinary tract. 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 VUR, the affected kidney functions poorly in most cases.

Secondary VUR is observed in at least 50% of patients with PUV [1235]. It is generally accepted that unilateral high-grade VUR associated with ipsilateral renal dysplasia acts as a 'pressure pop-off valve,' which would protect the contralateral kidney, leading to a better prognosis [1236]. Other types of pop-off mechanisms include large-bladder diverticula, urinary extravasation with or without urinary ascites, and a patent urachus [1237]. Protective effects of pop-off phenomena on renal function remain equivocal, however, as long-term outcomes from different studies have been discrepant, with some studies showing a protective effect [1238, 1239], while others have shown no protective benefit [1240-1242]. A possible explanation for such discrepancy could relate to differences in defining the exact nature of what constitutes a pop-off mechanism.

21.2 Classification systems of the urethral valves

Until today, the original classification by Hugh Hampton Young is the most commonly used classification [1243], which described three categories: type I, type II and type III. However, today, only type I and type III are found to be obstructive. Hampton Young's descriptions of type I and III 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 bulbomembranous junction [1243].

Type III

Has been found at various levels of the posterior urethra and apparently bears no relation to the verumontanum. This obstruction attaches to the entire circumference of the urethra, with a small opening in the centre [1233].

21.3 Diagnostic evaluation

During prenatal US screening, hydroureteronephrosis and a distended bladder are suspicious signs of a urethral valve. A thick-walled bladder appears to better predict PUV than a dilated posterior urethra ('keyhole' sign) [1244]. However, differentiation between obstructive and nonobstructive aetiologies on prenatal US is challenging, as both have a similar sonographic appearance [1245]. In the presence of increased echogenicity of the kidney, dilatation of the urinary tract and oligohydramnios, the diagnosis of a PUV should strongly be considered. Prenatal US is adequate in most cases (90%) [1246]. However, in some circumstances, when technical ultrasound conditions are poor, foetal MRI may provide additional information [1247].

Postnatally, creatinine, blood urea nitrogen and electrolytes should be monitored closely during the first few days. Initial management involving a multidisciplinary team including a paediatric nephrologist. The clinician must be aware of a noteworthy association between PUV and undescended testicles (UDT) and/or inguinal hernia [1248]. Undescended testicles occurred in 12-17 % of PUV, which is consistent with a tenfold increase [1249].

A VCUG (including lateral views of the urethra during the voiding phase without a catheter *in situ*) is recommended to assess the presence of a PUV. This study is essential whenever there is a question of an infravesical obstruction, as the urethral anatomy is well-outlined during voiding. The extent of posterior urethral deformity - as expressed by the posterior urethral height: width ratio - appears to correlate positively with nadir creatinine at twelve months of age [1250]. Nuclear renography with split renal function is important in assessing contributory renal function and/or scarring (DMSA or MAG3).

21.4 Management

21.4.1 ***Prenatal treatment***

Most cases of PUV are suspected prenatally [1233, 1251, 1252]. The potential for spontaneous resolution of bladder enlargement, and the timing of renal imaging are the main obstacles for prenatal intervention. As renal dysplasia is irreversible, it is important to identify those foetuses with good renal function [1253].

Prenatal interventions aim to restore amniotic fluid volume and attenuate the risk of pulmonary hypoplasia or further renal damage [1254]. The decision for prenatal intervention can be based on a staging system that is composed of renal ultrasonographic findings, amnion amount and foetal urine biochemistry [1252]. Early intervention (before the age of 16 weeks of gestation) may be beneficial for renal function. However, making the correct diagnosis and the detection of other severe comorbidities is extremely difficult currently [1255]. Later interventions are mostly of benefit for lung development, but not for renal function [1256]. There are, however, emerging reports of interventions as early as the end of first trimester, with results pointing to a potential preservation of long-term renal function. These reports are still preliminary. The techniques used are intricate and can be associated with a higher risk of foetal demise in these very frail and tiny patients [1257-1259].

Foetal urine samples before 23 weeks of gestation (ß2-microglobulin, sodium, chloride and calcium) may be helpful to distinguish between those who could benefit from intrauterine therapy and those in whom the outcome is most likely to be compromised [1260].

In a small study, normal biochemistry - a sodium level below 100mmol/L, a chloride value of < 90mmol/L, calcium < 8mg/dL, and ß2-microglobulin < 6mg/L obtained in the first foetal urine sample or biochemistry that improves between two sequential samplings, the latter scenario prompting foetal intervention - was associated with high foetal survival and normal renal function at five years [1261]. The status of amnion fluid, the appearance of the kidneys, as well as the foetal urine biochemistry may be helpful in counselling. Proteomic analysis of foetal urine using a signature peptide expressed in foetuses who go on to develop ESRD by the age of two years may show promise in assessing CLUTO. This should be considered as experimental.

The placing of a vesicoamniotic shunt (VAS) is a prenatal treatment designed to restore amniotic fluid cycling. A complication rate of 21-59% is reported, with dislocation of the shunt being the most common [1254]. The PLUTO trial (randomised study) failed to show a long-term benefit on renal function by placing a VAS [1262]. A meta-analysis on interventions for CLUTO reported that VAS resulted in a higher perinatal survival rate than conservative management (57.1% vs. 38.8%), with no significant differences in six-to-twelve-month survival, two-year survival or postnatal renal function [1263]. Foetal cystoscopy with laser ablation has a high complication rate without evidence for the effectiveness of these interventions [1264]. To avoid the severe complication of the laser ablation, balloon dilation has been tried [1265]. The number of patients and designs of these studies are insufficient to yield any recommendations. Parental information is very important and the natural history of CLUTO, including the postnatal outcomes with or without prenatal treatment, as well as the uncertainties and/or controversies regarding CLUTO diagnosis and treatment, should be discussed [1254].

21.4.2 ***Postnatal treatment***

Bladder drainage

Following delivery, the bladder should be drained transurethrally or suprapubically. This catheter drainage tube can then be used to perform a VCUG to confirm the diagnosis.

Valve ablation

When the neonate's medical situation has stabilised, the next step is to perform an endoscopic valve ablation, provided the urethra is accessible with available equipment. In cases in which the urethra is too small, urinary diversion should be maintained until valve ablation can be performed. Small paediatric cystoscopes and resectoscopes are available either to incise, ablate or to resect the valve at the 5, 7 and/or 12 o'clock 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. Two studies demonstrated a lower urethral stricture rate using the cold knife compared to diathermy [1266, 1267]. Currently, no strong evidence exists to support the use of laser ablation of PUVs. Preliminary studies on the use of Holmium YAG and Thulium lasers, show that laser fulguration is safe and effective [1268]. Within the three months following initial treatment, effectiveness of the treatment should be demonstrated either by clinical improvement (ultrasound and renal function), control VCUG or a re-look cystoscopy, depending on the clinical course [1269-1271].

Bladder neck incision

Bladder neck incision has been suggested as a means of managing secondary bladder neck obstruction [1272]. There is no current evidence which demonstrates that bladder neck incision has a role in preventing reintervention or rehospitalisation rates and therefore bladder neck incision cannot be recommended as a routine management option.

Vesicostomy

A vesicostomy is indicated if the child is too small to undergo endoscopic surgery, has failed endoscopic valve ablation, or has shown no clinical improvement following valve ablation. This is an alternative to prolonged catheter drainage and has been shown to stabilise/improve the upper tracts in up to 90% of cases [1273]. The most prevalent vesicostomy procedure in children was described by Blocksom and modified by Duckett [1274]. Key technical points are to ensure an adequate mobilisation of the bladder dome to enable a tension-free anastomosis with the fascia and skin. Common complication following vesicostomy are stomal stenosis, mucosal prolapse, peristomal dermatitis, and bladder calculi. The risk of prolapse is usually due to an extensive bladder mobilisation and due to too inferior placement of the stoma on the abdominal wall, allowing the posterior bladder wall to evert through the stoma.

High diversion

In cases in which bladder drainage is insufficient to prevent recurrent infections of the upper tract, improve renal function and/or a decrease upper tract dilatation, high urinary diversion should be considered. 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 its advantages and disadvantages [1275-1277]. Diversion can delay progression to end stage renal failure [1278].

Vesicoureteric reflux is very common in PUV patients (up to 72%) and is described bilaterally in up to 32% [1279]. A recent prospective observational study identified high-grade VUR as an independent risk factor for developing febrile UTIs, particularly in the first nine months of life. Therefore, antibiotic prophylaxis should be considered in such patients [1280]. Moreover, circumcision can be discussed to further reduce the risk of UTIs [1280]. In the above-mentioned multicentre, randomised, controlled trial, after two years of follow-up, this study demonstrated a statistically significant effect of circumcision as an adjunct to antibiotic prophylaxis in preventing febrile UTIs. The hazard ratio for developing a febrile UTI in the group with antibiotics alone was 10.3 (95% CI: 1.3-82.5) compared with the combined prophylactic antibiotics and circumcision group.

Early administration of oxybutynin may improve bladder function as shown in one study with eighteen patients [1281] and enhances resolution of hydronephrosis and VUR, as shown in a randomised controlled study of 49 patients. However, oxybutynin treatment had no discernible effect on renal function or risk of UTI [1272]. High-grade VUR is usually associated with a poorly functioning kidney, however, early removal of a nonfunctioning renal unit in an asymptomatic patient appears to be unnecessary. Deterioration of renal function without an anatomical obstruction and higher urine output (polyuria) may lead to an overdistension of the bladder during the night. Drainage of the bladder during the night by a catheter may be beneficial for the hydronephrosis, as well as for renal function [1282, 1283]. Patients with high daytime post-void residual urine volumes may benefit from clean intermittent catheterisation (CIC) [1284]. In those who do not want, or are not able, to perform CIC via the urethra, the placement of a catheterisable channel is a good alternative [1285].

Clean intermittent catheterisation has been shown to delay the onset of dialysis in patients with chronic kidney disease, progressing to ESRD, and has also resulted in significantly better ten-year graft survival rates in transplanted patients [1286, 1287].

21.5 Follow-up

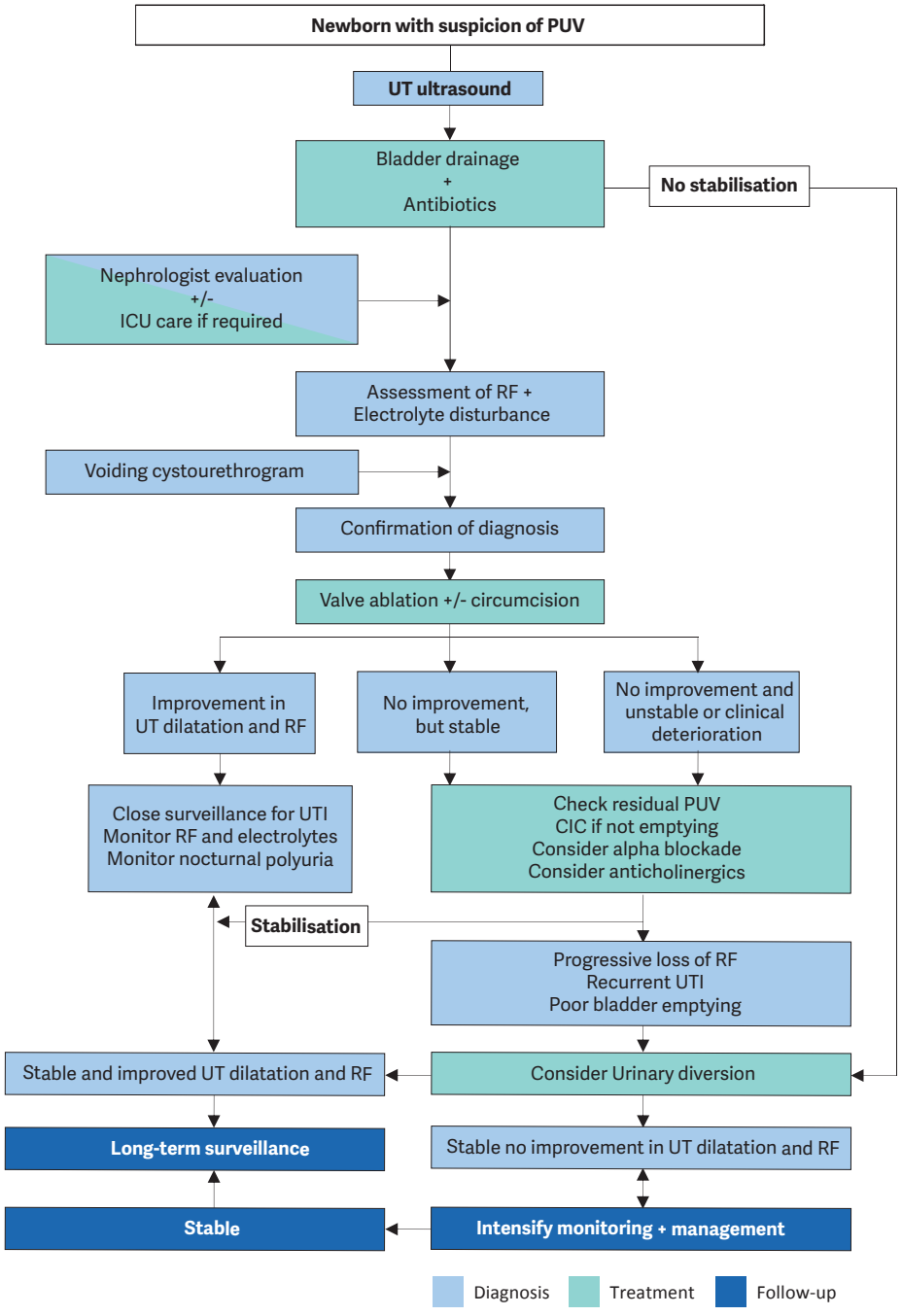
Several prognostic factors for the prediction of future renal function have been described. Various serum nadir creatinine levels are specified in the literature (0.85mg/dl to 1.2mg/dl [µmol/L]) [1250, 1288-1291]. Renal parenchymal quantity (total renal parenchymal area) and quality (corticomedullary differentiation and renal echogenicity) on initial postnatal US also have prognostic value [1292].

Life-long monitoring of these patients is mandatory, as bladder dysfunction ('valve bladder') is common, and the delay in day- and nighttime continence is a significant problem [1293]. Urodynamic studies play an important role in the management of patients with valve bladder, especially in those with suspicion of bladder dysfunction [1294, 1295], however, there is no consensus as to optimal timing or frequency of such studies. Poor bladder sensation and compliance, detrusor overactivity and polyuria (especially at night) and their combination are responsible for bladder dysfunction. In those with bladder overactivity, anticholinergic therapy can improve bladder function. In patients with poor bladder emptying, α-blockers can be used to reduce the post-void residual [1296, 1297].

Chronic kidney disease develops in up to 65% of PUV patients and approximately 20% of these progress towards ESRD [1298]. Renal transplantation in these patients can be performed safely and effectively [1299, 1300]. Deterioration of the graft function is mainly related to lower urinary tract dysfunction (LUTD) [1299]. Figure 14 provides an assessment and treatment algorithm.

Limited data is available pertaining to sexual function and fertility in patients with PUV. Long-term studies have demonstrated normal erectile function and fertility potential [1301, 1302]. However, a negative influence of the individual patient's fertility must be taken into account, as these patients have a higher risk for bilateral cryptorchidism, recurrent epididymitis and ESRD [1301].

Figure 14: An algorithm on the assessment, management and follow-up of newborns with possible PUV



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

Anterior urethral valve

Anterior urethral valve (AUV) is a semilunar or iris-like band of tissue on ventral aspect of urethra. It can be isolated or can be seen in association with anterior urethral diverticulum. The aetiology of isolated AUV is speculated to be secondary to congenital urethral obstruction, malunion of glandular and penile urethra, congenital cystic dilatation of periurethral glands, or ruptured distal lip of a syringocele [1303]. AUV can be present in the bulbous urethra, the penoscrotal junction and penile urethra. Patients may present with poor urinary stream, penile ballooning, UTI or haematuria. Firlit classified anterior urethral valves depending on the

presence of diverticulum and dilatation of urethra and upper tract [1304]. The diagnosis is based on a VCUG, with possible findings of dilated or elongated posterior urethra, dilatation of the anterior urethra, thickened trabeculated bladder, hypertrophied bladder neck, VUR and urethral diverticula. In doubtful cases, retrograde urethrography may be helpful showing linear filling defect along the ventral wall, or it may show a dilated urethra ending in a smooth bulge or an abrupt change in the calibre of the dilated urethra on VCUG [1305].

Treatment is mainly by means of endoscopic valve ablation. In selected patients, temporary diversion may be considered until the child is big enough for endoscopy. Open surgery is reserved for patients with very large diverticulum and defective spongiosum. Renal failure may develop in 22%, the risk being highest in patients with pretreatment azotaemia, VUR and UTI [1306].

Anterior urethral diverticulum

Common postnatal presenting features of anterior urethral diverticulum (AUD) are compressible ventral penile swelling, urinary postmicturition dribble, voiding difficulty, poor stream, and recurrent UTIs [1307-1309]. Diagnosis is by VCUG with or without a retrograde urethrogram. In small AUD, endoscopic cutting or deroofing of distal lip of the diverticulum can be sufficient treatment. Larger diverticulum requires excision with subsequent two-layered urethroplasty, or marsupialisation with staged urethroplasty. In cases of urosepsis and obstructive uropathy, a suprapubic catheter or temporary urinary diversion (vesicostomy or proximal cutaneous urethrostomy) may be indicated prior to definitive surgical management [1310, 1311]. Anatomically, AUVs have normal corpus spongiosum development, whereas AUDs do not [1311].

Syringocele

Cowper's glands are two bulbourethral glands that are located within the urogenital diaphragm which open into the urethra 1-2cm distal to the sphincter. Syringocele is the cystic dilatation of these glands. The aetiology can be congenital or acquired (trauma or infection). Syringocele has been classified as simple, imperforate, perforate and ruptured [1312]. A simpler grouping is suggested as to merge simple, perforated and ruptured syringocele into 'open syringocele' and imperforate to 'closed syringocele.' Closed syringoceles cause obstructive symptoms while open syringoceles act as a diverticulum and cause post-void dribbling and, in some case, obstruction [1313]. Depending on the syringocele type, patients can present with post-void dribbling, urethral discharge, UTI, perineal pain, haematuria, obstructive voiding symptoms, dysuria, or retention. Diagnosis is based on antegrade and/or retrograde urethrogram, which shows a cystic defect distal to prostate. If such studies are inconclusive, US and/or MRI may be used. Asymptomatic syringoceles can be managed conservatively. Endoscopic deroofing with various energy sources (cold knife, electrocautery and holmium laser) in both obstructing and non-obstructing syringoceles is an effective method of marsupialisation [1314]. In cases in which endoscopic approach is not feasible, open correction may be considered.

Cobb's collar

Cobb's collar is a congenital membranous stricture of the bulbar urethra. Unlike congenital obstructive posterior urethral membrane (COPUM), Cobb's collar is independent of the veru montanum and external sphincter and is believed to represent a persistence of part of the urogenital membrane [1315]. Voiding cystourethrogram shows narrowing in the proximal bulbar urethra with folds extending proximally, a dilated posterior urethra, prominent bladder neck and other findings of infravesical obstruction. Treatment with endoscopic cold-knife incision showed lower recurrence rates than electrocautery [1316].

Urethral atresia/hypoplasia

Male urethral atresia is congenital, complete obstruction of the urethra caused by a membrane that is usually located at the distal end of the prostatic urethra. The urethra distal to this point is usually hypoplastic, presumably from lack of foetal voiding [1317]. Urethral atresia is associated with bladder distention, VUR, hydronephrosis and renal dysplasia [1318]. Most cases reported have the phenotypic characteristics of the prune belly syndrome. Antenatal intervention may be beneficial in terms of foetal survival [1319]. Although progressive augmentation by dilating the urethra anterior (PADUA) procedure was described as a treatment modality, the majority of cases require some form of supravesical diversion [1317, 1318].

Posterior urethral polyps (PUP)

Although PUP does not cause antenatal hydronephrosis, it could cause obstruction later in life. Posterior urethral polyps is a polypoid, pedunculated, fibroepithelial lesion arising in the posterior urethra proximal to the veru montanum. The PUP lies on the floor of the urethra with its tip reaching into the bladder neck, and obstruction occurs due to distal displacement of the polyp during micturition [1320]. Patients complain of dysuria, haematuria and obstructive symptoms such as poor urinary stream and intermittent retention episodes. Diagnosis can be suspected by VCUG and/or US but is confirmed during cystourethroscopy. Treatment is

usually by endoscopic resection of the polyp. The course of the disease is benign, and no recurrences have been reported in the literature [1321, 1322].

21.6 Summary of evidence and recommendations for the management of posterior urethral valves

Summary of evidence	LE
Posterior urethral valves are one of the few life-threatening congenital anomalies of the urinary tract.	1b
Antenatal therapy could be considered based on ultrasound findings, foetal urine biochemistry, amniotic fluid level and chromosomal status.	4
Serum creatinine nadir above 0.85mg/dL is correlated with a poor prognosis.	2a
Neonatal circumcision as an adjunct to antibiotic prophylaxis in PUV patients significantly decreases the risk of developing febrile UTIs during the first two years of life.	1b
Early pharmacological management with oxybutynin may improve bladder function.	1b
Despite optimal treatment, 20% of patients will develop end stage renal disease.	2a
Renal transplantation in these patients is safe and effective if the bladder function is managed.	3

Recommendations	Strength rating
Drain the bladder in newborns with a suspected diagnosis of infravesical obstruction and place on antibiotic prophylaxis.	Strong
Perform a voiding cystourethrography in patients in whom a diagnosis of posterior urethral valves (PUV) is suspected.	Strong
Attempt endoscopic valve ablation after bladder drainage and stabilisation of the child.	Strong
Consider neonatal circumcision as an adjunct to antibiotic prophylaxis to decrease the risk of urinary tract infection in those with a PUV, particularly in the presence of high-grade vesicoureteral reflux.	Strong
Offer prolonged urinary diversion (suprapubic/transurethral) for bladder drainage if the child is too small for valve ablation.	Strong
Use serum creatinine nadir as a prognostic marker.	Strong
Assess split renal function by dimercaptosuccinic acid scan or mercaptoacetyltriglycine clearance.	Strong
Consider high urinary diversion if bladder drainage is insufficient to drain the upper urinary tract, or in the absence of clinical improvement.	Strong
Monitor and manage bladder and renal function lifelong.	Strong

22. RARE CONDITIONS IN CHILDHOOD

22.1 Urachal remnants

22.1.1 Introduction

The urachus is an embryonic structure arising as a result of the separation of the allantois from the ventral cloaca. The allantois appears on day 16 as a tiny, fingerlike outpouching from the caudal wall of the yolk sac, which is contiguous with the ventral cloaca at one end and the umbilicus at the other. The ventral portion of the cloaca develops into the bladder after cloacal division by the urogenital septum. Therefore, the bladder initially extends all the way to the umbilicus [1323]. With progressive foetal development, as the bladder descends towards the pelvis, the attachment between the umbilicus and the urachus becomes looser and the apical portion progressively narrows to a small, epithelialised, fibromuscular strand by the fourth or fifth month of gestation. The urachus then obliterates completely by birth, forming the median umbilical ligament [1324-1326]. The urachus varies from 3 to 10cm in length and from 8 to 10mm in diameter. It is a three-layered tubular structure, the innermost layer being lined with transitional epithelium, the middle layer composed of connective tissue, and the outermost muscular layer in continuity with the detrusor muscle [1327].

Urachal remnants (URs) originate from the failure of allantois obliteration, resulting in a urachal anomaly such as (1) urachal sinus, (2) urachal cyst, (3) vesicourachal diverticulum, or patent urachus [1324, 1325, 1328].

*22.1.2 **Epidemiology***

The reported prevalence of URs is highly variable, possibly due to the use of different definitions of URs. For example, in a study with patients undergoing laparoscopy for inguinal hernia repair, all visible residual tissue was scored as a UR, and therefore a UR was visualised in 35.4% of patients, particularly in patients <1 year (63.2%). All of these patients were asymptomatic [1329]. This supports a physiological regression of URs with age. In contrast, in a large study evaluating ultrasonographic exams in patients <18 years old with specific attention focussed on diagnosing URs, the prevalence of URs was only 0.2% [1330]. The incidence rate in boys is slightly higher than in girls [1331, 1332]. The subtypes of various URs reported in the literature is 10-48% for a patent urachus, 31-43% for a urachal cyst, 18-43% for a urachal sinus and 3-4% for a urachal diverticulum [1333, 1334].

*22.1.3 **Symptoms***

Most often, the UR is asymptomatic. The most common symptom of a urachal remnant is umbilical granulation, discharge and erythema in infants and abdominal pain in older children [1333]. A patent urachus can cause continuous or intermittent urine leakage from the umbilicus, causing umbilical granulation and erythema [1333]. A urachal cyst is usually diagnosed (1) incidentally, or (2) when it becomes infected causing abdominal pain and discharge of pus from the umbilicus or recurrent UTIs when it drains into the bladder. Other symptoms of infected urachal anomalies can vary from high fever and abdominal pain to urinary tract infections, LUTS and/or an abdominal mass [1334-1338]. A urachal diverticulum is often asymptomatic and is usually found incidentally during investigations for other problems. Urachal remnants can have associated or simultaneous anomalies. In one study, these anomalies were found in 17 of 46 children, of which VUR was the most common (six patients) [1339].

*22.1.4 **Diagnosis***

When a UR is suspected, a careful history and physical examination should be performed. In many patients, the diagnosis can be confirmed by US [1340]. However, in a retrospective study investigating 56 patients, the diagnostic accuracy of ultrasound to diagnose a UR or omphalomesenteric remnant in patients with umbilical discharge was shown to be relatively low (sensitivity 71.1%, specificity 72.2%, positive predicting value [PPV] 76.2%, negative predicting value [NPV] 66.7%) [1341]. An MRI or CT scan may be necessary in a minority of children for more detailed imaging [1337]. In general, a VCUG is only indicated when the child also presents with UTI or when the US shows signs of upper tract abnormalities [1342].

*22.1.5 **Treatment***

If a UR is symptomatic, the standard approach is the surgical removal of the remnant. However, in children less than six months old, even when they are symptomatic, a conservative approach with observation and/or antibiotics is possible, since there is a high chance of spontaneous resolution [1333, 1335, 1338, 1343, 1344]. In the event of active inflammation/infection, this should be treated first, and surgery should preferably be performed as an elective procedure. A Pfannenstiel, periumbilical or infraumbilical midline incision can be used for the open surgical approach [1336, 1345]. Alternatively, a laparoscopic or robotic approach has been shown to be safe and effective [1344, 1346-1348]. Complication rates can vary with age. In one study, it was shown that operative management of younger patients resulted in more reoperations, readmissions and longer length of stay [1349], while in another study, patients had fewer complications when surgery was performed at <1 year of age [1350]. Given that a conservative approach can be effective, it should precede an eventual surgical resection.

*22.1.6 **Pathology of removed remnants***

Removed specimens may show inflammation or a cystic structure [1335]. Patients presenting without symptoms are as likely to have epithelial elements in the UR as those presenting with symptoms [1337].

*22.1.7 **Urachal cancer***

Urachal cancer has not been shown to occur in children. Urachal anomalies are thought to be associated with an increased risk of bladder adenocarcinoma in adults, and urachal adenocarcinoma has an estimated incidence of 0.18 per 100,000 individuals yearly [1351]. In a large database study, the most frequent tumour type was adenocarcinoma (65-82%) followed by urothelial carcinoma (UC) (11-21%) [1352]. Five-year survival was 54.8-64.4%. Urachal adenocarcinoma is very rare, especially when one considers that up to 62% of children under sixteen years of age may have a UR [1340, 1353]. A study by Copp *et al.* found no association between the presence of UR symptoms and the presence or absence of epithelial tissue in pathology specimens, leading them to conclude that UR symptoms have poor predictive value for malignancy potential in these remnants

[1332, 1352]. Gleason *et al.* found that 5,721 URs would need to be excised to prevent a single case of urachal adenocarcinoma out of the nearly 65,000 patients reviewed [1351]. Assuming that epithelium is required in the development of urachal adenocarcinoma, the extrapolated number needed to treat (NNT) would be more than 8,000, as nearly 30% of urachal anomalies are void of an epithelial component. Fewer than 5% of urachal cancers have a nonepithelial origin such as sarcoma [1354]. At present, no long-term follow-up on untreated UR in children is available, and there is no evidence that urachal anomalies in children increase the likelihood of future malignancy [1333, 1355].

22.1.8 ***Summary of evidence and recommendation for management of urachal remnants***

Summary of evidence	LE
Most often, the urachal remnant is asymptomatic, but when symptomatic, the most common symptom of a urachal remnant is umbilical granulation, discharge and erythema in infants and abdominal pain in older children.	3
When a urachal remnant is suspected, a careful history and physical examination should be performed, and in many patients, the diagnosis can be supported by ultrasound.	3
Urachal remnants carry no known risk of malignant transformation during childhood and a very low overall lifetime risk.	3

Recommendations	Strength rating
Manage asymptomatic urachal remnants (UR) conservatively.	Strong
Manage symptomatic URs initially conservatively with observation and/or antibiotics, and preferably with elective surgical removal if persistent.	Weak
Remove symptomatic URs using either an open, laparoscopic or robotic approach.	Strong
Do not perform a voiding cystourethrography in an asymptomatic UR.	Weak

22.2 Papillary tumours of the bladder in children and adolescents (Papillary urothelial neoplasm of low malignant potential)

22.2.1 ***Incidence***

Papillary tumours of the bladder in children and adolescents are extremely rare and differ from papillary tumours in adults. A 'grape-like' papillary tumour in young children is more likely to represent rhabdomyosarcoma of the bladder, which is not the focus of this guideline. Papillary tumours in older children or adolescents will more likely be papillary urothelial neoplasms of low malignant potential (PUNLMP) [1356]. Children with risk factors such as previous bladder surgery and immunosuppressive medication can also develop a nephrogenic adenoma of the bladder, also presenting as a papillary tumour of the bladder.

22.2.2 ***Differences and similarities of papillary tumours of the bladder in children and adults***

Sex

The overall the risk of a papillary tumour in the bladder in paediatric and young adult patients is approximately double in males compared to females [1357].

22.2.3 ***Risk factors***

The majority of these patients have no identifiable risk factors [1358].

22.2.4 ***Presentation***

The most common symptom at presentation is monosymptomatic haematuria. Other less-common symptoms include abdominal pain, storage LUTS including frequency, dysuria and at times obstructive symptoms [1357].

22.2.5 ***Investigations and treatment***

Ultrasound of the genitourinary tract is the first investigation of choice. It is an excellent screening tool and can often accurately diagnose the nature and location of the lesion. In children and adolescents, a bladder US of the full bladder is more sensitive compared with adults due to reduced abdominal fat and thinner muscle layer [1359]. In the event of a need to differentiate the renal or bladder origin of the haematuria, a red blood cell morphology will reveal isomorphic blood cells, indicating a bladder origin. Urine cytology can be performed, however, it has very limited value, likely due to the low-grade nature of these tumours in children. If a bladder

tumour is suspected on imaging, cystoscopy should be performed for simultaneous diagnosis and treatment, as well as transurethral resection of the tumour. In children, cystoscopy requires general anaesthesia [1360].

*22.2.6 **Histology***

All the lesions in the paediatric and adolescent age group are identified as papillary and over 85% are solitary [1359]. Papillary bladder tumours in patients younger than twenty years of age have low-grade non-invasive disease (WHO classification) [1361]. These findings allow pathologists to conclude that, in children and adolescents, a papillary bladder tumour can be classified as papillary urothelial neoplasm of low malignant potential (PUNLMP). Papillary urothelial neoplasm of low malignant potential has minimal or no cytological atypia and differs from low grade urothelial carcinoma (UC), which has cytologic atypia, hyperchromatic nuclei and scattered mitosis and is rare in children but should always be considered [1362, 1363]. For optimal diagnosis and staging it is important that resection includes the detrusor. For resection technique and staging, see Chapter 22.1.

*22.2.7 **Additional treatment***

Despite lacking evidence, adjuvant instillations have been used sporadically in cases of paediatric UC [1357, 1358, 1364].

*22.2.8 **Prognosis, recurrence and surveillance***

Overall, the prognosis of papillary tumours of the bladder in children is good. The recurrence rate in children and adolescents varies from 8 to 15% [1356, 1357, 1359]. Mean time to recurrence can vary from 11 to 29 months depending on the study, with recurrences occurring up to 90 months from diagnosis, though 64% occur in the first year [1357]. In certain cases, recurrences can be aggressive [1359].

Follow-up strategies are based on the guidelines and protocols of papillary tumours of the bladder in adults. It is advised to follow-up children and adolescents with a history of a PUNLMP initially with a short interval of three to six months in the first year, and thereafter at least yearly, with urinalysis for haematuria and a US of the full bladder. In the event of sudden gross haematuria, the evaluation must be performed immediately. If the tumour was completely resected at primary surgery, standard follow-up cystoscopy is not necessary but should be performed in children or adolescents with any form of UC or suspected recurrence on bladder US [1359]. The exact duration of follow-up is unknown, but this Panel recommends follow-up for at least five years. Urine cytology has no place in follow-up. All cases should be managed in an MDT setting.

Inflammatory myofibroblastic tumours of the bladder (IMTB)

This type of tumour is rare, with nearly 200 cases reported in the literature [1365, 1366]. Approximately 25% occur in children with a median age at diagnosis of 7.5 years and a median tumour size of 5.5cm. Boys and girls are equally affected [1367]. These tumours are usually benign, with only very few reported malignant cases [1368]. Treatment is mostly surgical with transurethral resection, but local resection or partial cystectomy may be required in selected cases [1367, 1369]. Additionally, a conservative approach is reported [1370]. Histological examination is required to exclude other malignant tumours such as a rhabdomyosarcoma. In children, no recurrence has been reported so far. However, due to the malignant potential and few recurrences in adults, the same follow-up as for papillary bladder tumours is recommended.

Eosinophilic cystitis

Although well described in adults, the inflammatory condition eosinophilic cystitis is rare in the paediatric population, with fewer than 100 cases reported in the literature to date [1371]. Its aetiology remains unknown but is thought to be incited by immunoglobulin E-mediated attraction of eosinophils to the bladder wall, followed by mast cell degranulation. Eosinophilic cystitis has been linked to medications, specifically antibiotics such as penicillin, chemotherapeutic agents such as cyclophosphamide and mitomycin, and chronic bladder catheterisation [1372, 1373]. In children, as opposed to adults, males are more frequently afflicted, with seven years being the mean age of presentation. However, the condition can be seen throughout childhood even in LUTS [1371, 1374].

LUTS such as dysuria, frequency, urgency and incontinence are the most frequent and can mimic UTI [1375]. Other symptoms include haematuria, suprapubic tenderness and systemic symptoms. Obstructive manifestations due to mass formation in the bladder wall can result in ureteral obstruction leading to hydroureteronephrosis and suprapubic mass in infants in addition to voiding dysfunction [1371, 1374, 1376].

Although associated with allergy, only about a third of reported cases had a history of other allergic conditions, whereas half had significant eosinophilia or eosinophiluria. Diagnosis is often delayed as symptoms of

eosinophilic cystitis (EC) mimic other more common conditions such as UTI and LUTS, and most patients will ultimately have undergone imaging studies such as ultrasound, VCUG, CT and MRI, which while not specially diagnostic for the condition, may show bladder wall thickening or even mass formation, with rhabdomyosarcoma constituting an important differential diagnosis. A high index of suspicion for the diagnosis should therefore be maintained when dealing with protracted urinary symptoms not responsive to conventional intervention. Definitive diagnosis can only be attained on tissue biopsy obtained by cystoscopy. Histologically, eosinophilic infiltration of lamina propria and muscularis are seen in acute phases with >25 eosinophils per high power field considered to be significant [1371, 1374, 1376]. Management is not standardised. Removal of any possible allergens is the obvious first step and there are reports of self-limiting course of the disease. However, empirical treatment with corticosteroids, antibiotics, anticholinergics and antihistamines, in addition to cyclosporine A have been utilised and lead to resolution of symptoms in most cases. Partial cystectomy has been performed in circumscribed lesions that do not disappear spontaneously. No standard follow-up recommendations exist, however, surveillance is justified as recurrence has been reported in approximately a third of patients [1371, 1374].

Nephrogenic adenoma

Nephrogenic adenomas (NA) in children are rare benign lesions that usually occur in the setting of previous surgery or chronic irritation of the urinary tract [1377]. These benign proliferative lesions are most commonly found in the bladder. There is a significant predominance of girls compared to boys (5:1). The exact pathogenesis is unknown. It is proposed to be a metaplastic process of native urothelium in response to chronic injury. Recent evidence suggests that these cells can be derived from renal tubular cells that shed, migrate, reimplant and proliferate within urothelial mucosa [1378]. Although they are known to occur concurrently with bladder cancer, there are no *de novo* cases of bladder cancer diagnosed after nephrogenic adenoma. Previous history of bladder surgery such as bladder augmentation or presence of chronic inflammation or irritation is important [1379]. Lesions tend to develop at sites prone to chronic catheterisation injury. Other risk factors include trauma, immunosuppression and radiation. They present with haematuria and storage LUTS with a papillary/polypoid mass on cystoscopy. The recurrence rate is as high as 80% over four years [1377]. The final diagnosis is established by cystoscopy and histopathological review of biopsy specimen. Treatment is excision either by transurethral resection (which often requires reresections), open excision or partial cystectomy. Again, no standard follow-up recommendations exist. However, regular follow-up with cystoscopy has been advocated, particularly for patients with augmented bladders, because recurrence seems particularly high in this subgroup [1379].

22.2.9 Summary of evidence and recommendations for papillary tumours of the bladder in children

Summary of evidence	LE
The majority of paediatric patients have no identifiable risk factors for bladder tumours.	3
There is no evidence on intravesical therapy for bladder tumours in children and adolescents.	4
Overall, prognosis of papillary tumours of the bladder in children is good.	3
Inflammatory myofibroblastic bladder tumours are usually benign.	3
A third of paediatric eosinophilic cystitis (EC) cases are associated with a history of allergic conditions and 50% are associated with significant eosinophilia or eosinophiluria.	4
Paediatric EC patients usually present with irritative and or obstructive urinary symptoms, which can mimic UTI or LUTS, thereby leading to delayed diagnosis.	4
In paediatric EC, definitive diagnosis can only be attained on tissue biopsy obtained by means of cystoscopy.	4
In EC, treatment with corticosteroids, antibiotics, anticholinergics and antihistamines, in addition to cyclosporine A, have been utilised and lead to resolution of symptoms in most cases.	4
No standard follow-up recommendations exist, however, surveillance is justified as recurrence has been reported in approximately a third of patients.	4
Nephrogenic adenoma in children are rare benign lesions that usually occur in the setting of previous surgery or chronic irritation of urinary tract and mainly occurring in the bladder.	4
Nephrogenic adenoma usually presents with haematuria and or storage LUTS and with a papillary/polypoid mass seen on cystoscopy.	4
Nephrogenic adenoma diagnosis is established by cystoscopy and histopathological review of biopsy specimen.	4

Nephrogenic adenoma treatment is excision either by transurethral resection (which often requires reresections), partial cystectomy or open excision.	4
Nephrogenic adenoma A recurrence rate is high, therefore justifying regular follow-up.	4

Recommendations	Strength rating
Ultrasound is the first investigation of choice for the diagnosis of paediatric bladder tumours.	Strong
Cystoscopy should be reserved if a bladder tumour is suspected on imaging for diagnosis and treatment.	Strong
After histological confirmation, inflammatory myofibroblastic bladder tumours should be resected locally.	Weak
Follow-up should be every three to six months in the first year, and at least annually thereafter, with urinalysis and an ultrasound for at least five years.	Weak
Have a high index of suspicion of eosinophilic cystitis (EC) in protracted urinary tract symptoms unresponsive to regular treatment.	Strong
Remove any possible allergens as the obvious first step in managing EC.	Strong
Eosinophilic cystitis can be managed medically with corticosteroids, antibiotics, anticholinergics and antihistamines, in addition to cyclosporine A.	Weak
Manage nephrogenic adenoma (NA) by resection either transuretherally or by open excision.	Strong
Regular endoscopic follow-up especially for augmented patients with NA is justified.	Weak

22.3 Penile rare conditions

Paediatric lesions of the penis are uncommon, but an important part of the paediatric urological practice. The most common of these lesions are cystic penile lesions followed by vascular malformations and neurogenic lesions [1380]. Soft tissue tumours of the male external genitalia are uncommon but have been described in the paediatric age group and can be malignant [1381].

22.3.1 Cystic lesions

Epidermal inclusion cysts

Epidermal inclusion cysts are the most common genital cystic lesion and can occur anywhere on the body in both men and women. In the penis, these types of cysts occur most commonly over the penile shaft, varying from 0.1 to 1cm in diameter. The epithelium of these cysts is lined and filled with keratin. It is a painless swelling and can present in the age group with a history of circumcision. Treatment by total surgical excision is mainly indicated for cosmetic or symptomatic (e.g. infection) reasons and should be performed without rupturing the cyst to avoid recurrence [1382].

Mucoid cyst of the penis

Mucoid cysts are synonymous with parameatal cyst or genitoperineal cyst of median raphe. Mucoid cysts are midline developmental cysts arising from ectopic urethral mucosa filled with mucoid material. These types of cysts present starting at birth but are usually detected during adolescence or later. These cysts are usually asymptomatic, developing over the penile ventral surface around the glans and require surgical removal for either cosmetic, functional or symptomatic reasons [1383].

Median raphe cysts

These types of cysts arise from incomplete closure of the genital fold during embryogenesis; they are commonly diagnosed in the first decade of life but can present later as they tend to be asymptomatic [1384]. They are either unilocular or multilocular fluid containing cysts, with a mean size of 0.8cm, but cysts larger than 2cm have also been reported [1385]. Cysts are centred in dermis, with no connection to urethra or epidermis. Histopathologically, there are four types: urethral (urothelium-like epithelium, account for 55% cases), as well as epidermoid, glandular and mixed. Epidermoid cysts may be congenital or acquired. Acquired penile epidermoid cysts (PECs) occur by traumatic implantation of the epidermal components into the dermis, usually as a result of surgical procedures such as circumcision and hypospadias repair [1386].

Median raphe cysts can be treated conservatively and can resolve spontaneously or persist. Cyst aspiration is associated with high risk of recurrence and surgical excision is the treatment of choice. Although most penile cysts are asymptomatic, these types of cysts may become infected, resulting in pain and tenderness. They can also present with ulceration, rupture and urinary obstruction if they are close to the urethral meatus. This, along with cosmetic issues, leads most caregivers and patients to opt for surgical excision.

Smegmal cysts or smegmal pearls

Smegmal cysts can be a differential for aforementioned cysts. Smegmal cysts are a benign collection of smegma in the subpreputial space in uncircumcised boys with anticipated spontaneous resolution [1387].

Dermoid cysts

Dermoid cysts are congenital, asymptomatic, firm, solitary, subcutaneous cystic lesions occurring commonly in the region of the corona involving the foreskin. Histopathologically, these types of cysts contain sweat and sebaceous glands, with elements of hair and squamous epithelium. Pilosebaceous cysts have been described on the glans. These cysts are benign and usually diagnosed after excision.

*22.3.2 **Vascular malformations***

A broad classification of penile vascular lesions into haemangiomas and vascular malformations was proposed by Ramos in 1999 [1388]. Haemangiomas develop rapidly at birth and involute slowly. Venous malformations are usually present at birth and slowly progress [1389]. Haemangiomas also include pyogenic granulomas, which are benign outgrowths of cutaneous capillary vessels formed usually from chronic irritation [1380]. The growth cycle of infantile haemangiomas is divided into early and late proliferative stages, followed by a slow involution phase, completing growth by the age of nine months [1390]. Propranolol (oral or topical) is currently first-line treatment for infantile haemangiomas. The exact mechanism of action is unknown but can include inhibition of angiogenesis and vasoconstriction, among others. The dose is in the range of 1.5-2.5mg/kg, which must be continued for 12 to 18 months and then tapered through active or passive weaning to reduce risk of rebound growth [1390]. Other factors leading to rebound growth after propranolol treatment include deep haemangiomas, which occur in approximately 38% of patients despite propranolol therapy, requiring local therapy such as topical timolol, pulsed dye laser or intralesional steroids. After twelve months, the median improvement with treatment is reported as 81% (range 70-90%), based on VAS scores of serial patient photographs.

Vascular malformations are congenital lesions of capillary, lymphatic and venous (or slow-flow) or arterial/arteriovenous (fast-flow) origin that enlarge slowly as the patient grows. These malformations include glomus tumours, which are primarily congenital arteriovenous shunts that develop from thermoregulatory glomus bodies (fast-flow vascular malformations). Glomus tumours of the penis can arise on the glans penis, corpora of the penis and as periurethral masses, sometimes accompanied by glomus tumours of fingers and feet [1391]. These are usually asymptomatic at presentation or may have symptoms such as priapism, palpitation and perineal pain. Glomus tumours are benign despite exhibiting high-grade nuclear polymorphism. Vascular malformations are usually benign and managed conservatively. Treatment options include LASER, sclerotherapy [1389] or surgical excision [1392].

In the treatment of children's penile venous malformations, relatively conservative and mild sclerosing agents, such as polidocanol, pingyangmycin or bleomycin, are recommended [1389]. However, glomus tumours specifically need surgical treatment and follow-up due to the risk of recurrence from incomplete excision [1393].

*22.3.3 **Neurogenic lesions***

Penile neurofibroma (PNF) is an extremely rare lesion arising from perineural and Schwann cells and usually occurs with evidence of systemic neurofibromatosis or Von Recklinghausen syndrome [1394]. Neurogenic lesions are successfully treated with complete excision [1380]. It should be noted that penile schwannomas in children may differ from those in adults, as they may grow faster and be bound up with genetic syndromes or certain specific tumours that affect intelligence [1395].

Rare cases of malignant schwannomas on the penis, presumably secondary to malignant transformation of benign neurofibromas, have been reported in boys with a strong family history of neurofibromatosis. This type of malignant degeneration of neurofibromatosis reportedly occurs in 5-16% of children [1394]. Therefore, these patients require long-term follow-up due to risk of recurrence, new tumour formation and malignant transformation.

*22.3.4 **Soft tissue tumours of penis***

Mesenchymal tumours are rare in the external genitalia, and they require excision to differentiate between benign and malignant neoplasms. Histopathological characterisation is essential to ensure that malignant tumours receive radical treatment with adjuvant therapy or close follow-up [1381].

Presentation is usually of a painless penile mass that is nontender and rubbery upon examination. Ultrasound may be useful in characterising the lesion but is not diagnostic. The ultrasound can exclude urethral invasion if it is close to the urethra [1381]. Once an excision biopsy is performed, if aggressive malignant components are found, a further wider resection may be required.

Fibrosarcoma is a rare, non-rhabdomyosarcoma soft tissue tumour that arises from fibrous tissue. The infantile form of fibrosarcoma is rare and those occurring on the penis are even rarer in the paediatric age group. Surgical intervention has a favourable prognosis in the paediatric age group, with long-term survival of 90% in sporadic cases [1396]. Myofibroma is a benign congenital lesion that occurs either as a solitary lesion or as a part of myofibromatosis with multiple soft tissue tumours. Excision is necessary for histological diagnosis [1381].

Primary penile teratomas are an extremely rare subtype of congenital germ cell tumours, and they tend to be asymptomatic and are subdermal on US with no blood flow on Doppler [1397]. These teratomas require aggressive treatment with surgical resection due to their unpredictable behaviour and unresponsiveness to chemotherapy. Mature teratomas are benign, but immature teratoma, or even mixed teratomas with immature components, can turn malignant and have the potential to metastasise and recur.

22.3.5 ***Penile lymphedema***

Lymphedema in adults is usually secondary to malignancy or infectious disease affecting lymphatic drainage. In the paediatric age group, however, lymphedema is usually primary and generally very rare, affecting 1.2 per 100,000 persons under the age of 20 years [1398]. Of these, only a very small fraction relates to the genital region. Regardless of underlying aetiology, inefficient lymphatic drainage leads to accumulation of subcutaneous lymph, which causes tissue swelling and inflammation. This in turn stimulates adipose deposition and fibrosis, further exacerbating enlargement. With time, the oedematous tissue becomes vulnerable to infection, chronic cutaneous changes and disfigurement [1399]. Additionally, when occurring in the genital region, urological complications may ensue, such as phimosis, haematuria, bleeding, bladder outlet obstruction, pain, dysuria, lymphorrhea and severe psychological distress due to resultant deformity [1400, 1401].

In the largest cohort of male genital oedema in the paediatric age group, 92% of cases were primary. Of these, only 25% had a discernible familial or syndromic association, such as Noonan syndrome, lymphedema-distichiasis or Milroy disease [1400]. Secondary genital lymphedema in children has been reported after inguinal surgery and noncaseating granulomatous lymphangitis as seen with metastatic Crohn's disease [1400-1402]. Average age of onset was reported to be from 4.5 to ± 6.3 years, with 61% of cases presenting in infancy, 13% in childhood and the remaining 26% in adolescence. Oedema is usually penoscrotal in 72% of cases, isolated scrotal in 24% and very rarely confined exclusively to the penis in 4%. Moreover, concomitant lower limb oedema is the rule in two-thirds of cases [1400].

There is no general consensus on diagnostic workup of these patients. History and physical examination (including family history) is usually sufficient. However, lymphoscintigraphy can be used as a confirmatory test, more so for limb than genital oedema, where results can be difficult to interpret [1400]. Ultrasonography is nonspecific but has been advocated by some to exclude secondary lymphedema by examining the patency of iliac and caval vessels [1403]. Magnetic resonance imaging is useful to exclude other differential diagnoses, such as other venous or lymphatic anomalies [1400].

Conservative treatment is the accepted first-line treatment. The mainstay is compression therapy to maintain and prevent further swelling. This can be achieved by compression stockings and undergarments. Additionally, close observation and protection of the skin to prevent excoriations and infection is essential [1400, 1403]. Compression therapy is, however, less effective on genital oedema than it is on limb oedema, particularly in growing children. When conservative management fails, and particularly in symptomatic cases, or in patients with functional impairment, surgical debulking may be necessary. This can either take the form of circumcision in cases in which the foreskin is affected or excision of affected skin and subcutaneous tissues with restructuring and contouring for optimal cosmetic outcome. Complete skin excision and grafting may also be required [1400-1403]. Surgical management can be challenging and must be restricted to patients with significant symptoms. Complications include recurrences, continuous lymphatic leakage, haematoma, infection and poor cosmetic outcome [1398, 1403, 1404].

Summary of evidence	LE
Cystic penile lesions are the most common paediatric penile lesions, followed by vascular malformations and neurogenic lesions.	3
Neurofibroma patients require long-term follow-up due to risk of recurrence, new tumour formation and malignant transformation.	3
Mesenchymal tumours are rare and require excision to differentiate between benign and malignant neoplasms.	3

Recommendations	Strength rating
Treatment of penile cystic lesions is by total surgical excision. It is mainly indicated for cosmetic or symptomatic reasons, e.g. infection.	Weak
Propranolol is currently first-line treatment for infantile haemangiomas.	Strong
Conservative management is the first-line treatment for penile lymphedema.	Strong
In symptomatic cases or in patients with functional impairment, surgical intervention may become necessary for penile lymphedema.	Weak

23. EMERGENCIES IN PAEDIATRIC UROLOGY

23.1 Acute scrotum

Refer to Chapter 8 on acute scrotum.

23.2 Paraphimosis

Refer to Chapter 3 on phimosis and other abnormalities of the penile skin.

23.3 23.3 Priapism

*23.3.1 **Epidemiology, aetiology and pathophysiology***

Priapism is a prolonged full or partial erection of the penis unrelated to sexual stimuli lasting ≥ 4 hours. Although the prevalence of priapism in children is not well-reported in literature, it is considered a rare disease. The most common cause of priapism in children is sickle cell disease (SCD), which accounts for approximately 65% of all cases, followed by leukaemia (10%), trauma (10%), idiopathic (10%) and drugs (5%) [1405]. In patients with SCD, the mean age of the first episode of priapism has been shown to be 15 years old, with 25% presenting prepubertally [1406].

*23.3.2 **Classification***

Priapism in children can be divided in four groups: ischaemic (low-flow) priapism, stuttering priapism, nonischaemic (high-flow) priapism, and neonatal priapism.

Ischaemic (low-flow, veno-occlusive) priapism is the most common form (95%) in children. It presents as a painful, rigid erection, with decreased or absent intracavernous arterial inflow. This is considered a medical emergency, since a duration of ≥ 4 hours can cause ischaemia within the corpora cavernosa, and eventually irreversible damage, such as smooth muscle necrosis, corporal fibrosis and erectile dysfunction [1407].

Stuttering priapism presents as recurrent, self-limiting, prolonged erections, with intervening periods of detumescence. This often precedes an episode of ischaemic (low-flow) priapism [1408].

Non-ischaemic (high-flow, arterial) priapism is a prolonged erection of the penis lasting ≥4 hours not associated with ischaemia. The most common cause is penile, perineal or pelvic trauma, which can lead to the development of an arteriolar-sinusoidal or arteriocavernous fistula, and usually has a delayed presentation after trauma (three hours to seven days) [1409].

Neonatal priapism is a very rare condition, with only a few case series described in literature. The conditions presents as a prolonged erection of the penis ≥4 hours in a newborn. Sickle cell disease is not associated with neonatal priapism, due to the presence of foetal haemoglobin. Neonatal priapism is most commonly idiopathic, but polycythaemia is the most common cause among the identifiable causes [1410]. It also has a favourable natural history and benign pathophysiology.

*23.3.3 **Diagnostic evaluation***

History

A comprehensive history is critical in priapism and can determine the underlying priapism subtype and cause. Table 8 presents key points in the history of a child with priapism.

Table 8: Key points in the history for a child with priapism (adapted from Broderick *et al.* [1411])

Duration of erection
Presence and severity of pain
Previous episodes of priapism and methods of treatment
Medications or recreational drug use
Sickle cell disease, haemoglobinopathies, hypercoagulable states, vasculitis
Trauma to the pelvis, perineum or penis

Physical examination

Inspection and palpation of the penis is recommended to assess the degree of tumescence and rigidity and the involvement of the corpora cavernosa, spongiosum and glans. In ischaemic (low-flow) priapism, typically the glans and corpus spongiosum are flaccid. In nonischaemic (high-flow) priapism, typically the corpora and the glans are tumescent, but not fully rigid (Table 9). If perineal compression results in detumescence, this is suggestive of a non-ischaemic (high-flow) priapism.

Penile imaging

Colour doppler ultrasonography of the penis and perineum should be performed in all patients. This can support clinical differentiation between ischaemic (low-flow) and nonischaemic (high-flow) priapism with 100% sensitivity and 73% specificity in adults [1412], where a peak systolic velocity <50cm/s and a mean velocity <6.5cm/s are suspicious for ischaemia [1413].

Laboratory testing

Laboratory testing with complete blood count (white blood cell count with blood cell differential platelet count) and specific tests for SCD or other haemoglobinopathies should be performed. When ischaemic (low-flow) priapism is suspected, penile blood gas analysis should be performed to differentiate between ischaemic (low-flow) and non-ischaemic (high-flow) priapism (Table 10). However, when non-ischaemic (high-flow) priapism is suspected, penile blood gas analysis should not be the diagnostic of first choice, due to the invasive nature and need for anaesthesia.

Table 9: Key findings in paediatric priapism (adapted from Donaldson *et al.*, and Broderick *et al.* [1405, 1411])

	Ischaemic (low-flow) priapism	**Non-ischaemic (high-flow) priapism**
Corpora cavernosa fully rigid	Typically	Seldom
Penile pain	Typically	Seldom
History of stuttering priapism	Typically	Seldom
Haematological abnormalities	Typically	Seldom
Abnormal penile blood gas	Typically	Seldom
Perineal trauma	Seldom	Typically

Table 10: Blood gas analysis (adapted from Broderick *et al.* [1411])

Source	pO_2 (mmHg)	pCO_2 (mmHg)	pH
Normal arterial blood (room air) (similar values are found in nonischaemic priapism)	> 90	< 40	7.40
Normal mixed venous blood (room air)	40	50	7.35
Ischaemic priapism (first corporal aspirate)	< 30	> 60	< 7.25

*23.3.4 **Disease management***

Differentiation between ischaemic (low-flow) and non-ischaemic (high-flow) priapism is essential since clinical management differs between the two. Ischaemic (low-flow) priapism is a medical emergency requiring immediate treatment, where non-ischaemic (high-flow) priapism does not. The management of a child with ischaemic (low-flow) priapism is in most parts similar to adults [1414].

Ischaemic (low-flow) priapism

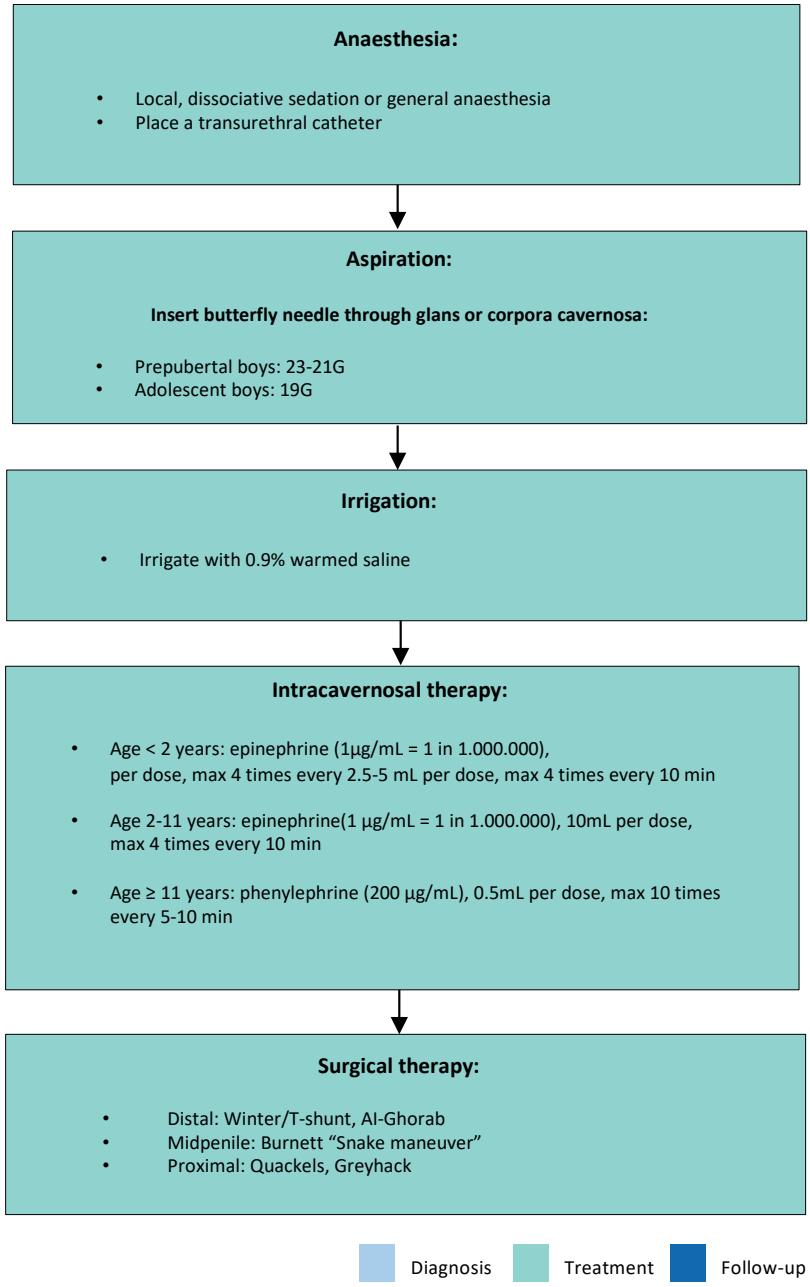
Conservative

Although the amount of evidence is low, conservative treatment should be advised (e.g. physical exercise, urination, cold bath, ejaculation, oral/IV fluids and analgesia), however, if symptoms persist ≥2 hours, urgent medical care should be sought [1415].

Medical

If conservative treatment fails, a step-up approach should be used for the management of priapism [1405]. Firstly, anaesthesia should be given for the child - either local anaesthesia, dissociative sedation or general anaesthesia, depending on the availability of paediatric anaesthetic expertise and the age and condition of the child. In SCD, there are increased risks for general anaesthesia that should be taken into account [1416]. Subsequently, a step-up approach should be used for treatment (Figure 15), adapted from Donaldson and the adult priapism guideline [1405, 1414].

Figure 15: Step-up approach for the management of Ischaemic (low-flow) priapism in children



Nonischaemic (high-flow) priapism

Nonischaemic (high-flow) priapism is a very rare entity in the paediatric population. The treatment of nonischaemic (high-flow) priapism is not emergent. One study demonstrated that conservative management and long-term follow-up yielded no evidence of erectile dysfunction after a median follow-up of 55 months [1417]. Conservative treatment, such as perineal compression or application of ice to the perineum, can be successful. If symptoms persist, super-selective angioembolisation can be performed, however, this is technically challenging in children and requires a specialist paediatric vascular radiologist [1418]. Children should be initially treated with conservative management, reserving embolisation for refractory cases [1419].

Stuttering priapism, and priapism associated with sickle cell disease (SCD)

The management of a prolonged erection in stuttering priapism is similar to ischaemic (low-flow) priapism. Further management should focus on the prevention of further episodes. Several agents are proposed in literature, such as α-adrenergic agonists, PDE-5 inhibitors, hydroxyurea, β-agonists or gonadotropin-releasing hormone agonists, but evidence is limited.

The acute management of SCD priapism is closely related to that outlined above. The main caveat is that those with SCD should have their disease medically optimised in close conjunction with paediatric haematology/oncology through a multidisciplinary approach. Hydroxyurea may decrease crisis frequency and severity in SCD-associated priapism [1420]. Unlike urgent surgical management performed in the adult population, a minimally invasive management strategy can be implemented in the paediatric population, where an extended period of conservative management that avoids operative management under general anaesthetic can be effective in approximately 60% cases [1421].

Neonatal priapism

Neonatal priapism is usually self-limiting and rarely requires treatment. Careful observation is appropriate in most cases since the majority resolve spontaneously without sequelae. If underlying polycythaemia is present, this could be treated by venesection and fluid resuscitation [1422].

23.4 Summary of evidence and recommendations for the diagnosis and management of priapism

Summary of evidence	LE
The most common cause of priapism in children is sickle cell disease.	3
Ischaemic (low-flow, veno-occlusive) priapism is the most common form (95%) in children and is considered a medical emergency.	3
Colour doppler ultrasonography of the penis and perineum can support clinical differentiation between ischaemic (low-flow) and nonischaemic (high-flow) priapism in children.	2b

Recommendations	Strength rating
Perform a doppler ultrasonography in all patients presenting with priapism.	Strong
In children with ischaemic (low-flow) priapism, perform a full blood count and haemoglobinopathy screen to exclude sickle cell disease or other haematological disorders.	Strong
Adopt a multidisciplinary approach when managing patients with SCD-associated priapism.	Strong
Use a stepwise approach starting with the least invasive therapy in patients with ischaemic (low-flow) priapism.	Strong
Manage neonatal and non-ischaemic (high-flow) priapism conservatively in the initial management period.	Strong

24. PAEDIATRIC UROLOGICAL TRAUMA

Trauma is the leading cause of morbidity and mortality in children [1417]. Trauma is generally caused by either blunt injuries from falls, car accidents, sports injuries, physical assault or sexual abuse, or penetrating injuries, usually due to falls onto sharp objects or from gunshot or knife wounds.

24.1 Paediatric renal trauma

24.1.1 Epidemiology, aetiology and pathophysiology

Of all renal injuries, approximately 25% occur in children, 79% of which are low-grade (I, II or III) and 21% of which are high-grade (IV or V) [1418]. The most common cause of renal injury is blunt abdominal trauma (90%), in which the kidney is the most commonly affected organ, accounting for approximately 10% of all blunt abdominal injuries [1419]. Children are more likely than adults to sustain renal injuries after blunt trauma due to several anatomical factors, including decreased perirenal fat, weaker abdominal musculature, a relatively large size of the kidney in relation to the rest of the body, foetal lobulations which result in a higher likelihood of a local parenchymal disruption, and a less-ossified rib cage [1423]. Blunt renal trauma is also frequently associated with injury to other organs [1424].

*24.1.2 **Classification systems***

Renal injuries are classified according to the kidney injury scale of the American Association for the Surgery of Trauma (Table 11) [1425].

Table 11: Renal injury classified according to the kidney injury scale of the American Association for the Surgery of Trauma [1425]

Grade	Type of injury	Description
I	Haematoma and/or contusion	Subcapsular haematoma and/or parenchymal contusion without laceration.
II	Haematoma	Perirenal haematoma confined to Gerota's fascia.
	Laceration	Renal parenchymal laceration ≤ 1cm depth without urinary extravasation.
III	Laceration	Renal parenchymal laceration > 1cm depth without collecting system rupture or urinary extravasation.
	Vascular	Any injury in the presence of a kidney vascular injury or active bleeding contained within Gerota's fascia.
IV	Laceration	• Parenchymal laceration extending into urinary collecting system with urinary extravasation; • Renal pelvis laceration and/or complete ureteropelvic disruption.
	Vascular	• Segmental renal vein or artery injury • Active bleeding beyond Gerota's fascia into the retroperitoneum or peritoneum; • Segmental or complete kidney infarction(s) due to vessel thrombosis without active bleeding.
V	Laceration	Shattered kidney with loss of identifiable parenchymal renal anatomy.
	Vascular	• Main renal artery or vein laceration or avulsion of hilum • Devascularised kidney with active bleeding.
Vascular injury is defined as a pseudoaneurysm or arteriovenous fistula and appears as a focal collection of vascular contrast that decreases in attenuation with delayed imaging. Active bleeding from a vascular injury presents as vascular contrast, focal or diffuse that increases in size or attenuation in delayed phase. Vascular thrombosis can lead to organ infarction. Grade based on highest grade assessment made on imaging, at operation or on pathologic specimen. More than one grade of kidney injury may be present and should be classified by the higher grade of injury. Advance one grade for bilateral injuries up to Grade III.		

*24.1.3 **Diagnostic evaluation***

In a child who has sustained blunt abdominal trauma, renal involvement can often be suspected from the history, physical examination and laboratory evaluation. Renal involvement may be associated with abdominal or flank tenderness, lower rib fractures, fractures of vertebral pedicles, trunk contusions and abrasions, and haematuria. Vital signs should be monitored during the initial evaluation and give the most reliable indication of the urgency of the situation. It is important to consider that children, unlike adults, are able to maintain their blood pressure, even in the presence of hypovolaemia, due to compliance of the vascular tree and mechanisms for cardiac compensation [1420]. All the clinical aspects involved must be considered, including the history, physical examination, consciousness of the child, overall clinical status and laboratory findings to decide on the diagnostic algorithm and whether or not a child requires further imaging studies. In severe renal injuries, 65% of patients suffer gross haematuria and 33% non-visible haematuria, while 2% have no haematuria at all [1421]. There have been several reports of significant renal injuries that manifest with little or even no blood in the urine [1422].

24.1.3.a Choice of imaging method

FAST ultrasound

In severe trauma or haemodynamically instable patients, focussed assessment sonography in trauma (FAST) ultrasound can be used to identify a hemoperitoneum with high specificity (95%) but low sensitivity (33-89%)

and negative predictive value (50%). However, sensitivity and specificity for kidney trauma and retroperitoneal haemorrhage is low. Therefore, it is not recommended as a sole diagnostic tool [1426].

Computed tomography

Computed tomography scanning is the imaging modality of choice in patients with suspicion of renal injuries, since it is widely available, quick and provides accurate grading [1427]. Ideally, CT is performed in three phases: the arterial phase to detect vascular injury or active bleeding, the nephrogenic phase to detect parenchymal lacerations, and the delayed phase to detect injury of the collecting system or ureter. Moreover, CT scanning can detect associated other intra-abdominal injuries, which are frequently associated with renal trauma, particularly in grade III-V [1424]. Scanning protocol should be adapted for paediatric patients according to the principles of ALARA (as low as reasonably achievable) to reduce the amount of ionising radiation as much as possible.

Ultrasound

(Contrast-enhanced) US can be considered as the sole investigation in patients with mild symptoms and no other indications for CT scanning, where the mechanism of trauma and the condition of the patient do not suggest the presence of injury to other organs or the urinary tract. Although conventional US is not sufficiently accurate to grade renal trauma, there could be a role for contrast-enhanced ultrasound (CEUS) to identify parenchymal lesions. However, this technique cannot detect injuries to the urinary tract or collecting system, since the contrast agent is not excreted by the kidney [1428]. Ultrasound can be performed in follow-up of a renal trauma to reduce the amount of radiation. However, even in high-grade renal trauma, routine repeat imaging may be avoidable in stable, asymptomatic patients [1429].

*24.1.4 **Disease management***

The modern management of trauma is multidisciplinary, requiring paediatricians, emergency physicians, surgeons, urologists and other specialties as necessary.

Nonsurgical conservative management with bed rest, fluids and monitoring has become the standard approach for treating blunt renal trauma. In high-grade renal injuries, a conservative approach is effective and recommended for hemodynamically stable children [1430]. However, this approach requires close clinical observation and intermittent reassessment of the patient's overall condition. Therefore, a good initial trauma CT with delayed images to check for urinary extravasation is recommended, since patients with a urine leak have higher rates of morbidities, including febrile episodes and an increased requirement of operative or image-guided interventions [1431]. However, early drainage does not seem to prevent persistent urinary extravasation or complications [1432]. Therefore, reserve stenting and/or percutaneous drainage only when the patient is symptomatic [1433]. Emergency intervention is indicated only for haemodynamic instability and angioembolisation, if available, for ongoing or delayed bleeding is preferred compared to open surgery. The results of angioembolisation were evaluated and were successful in 92% of patients with Grade III-IV (294/322) and 76% of Grade V (63/82) injuries. Moreover, the success rate was 90% (312/346) in hemodynamically stable patients, but only 63% (42/66) in hemodynamically unstable patients [1434]. Absolute indications for surgery include persistent bleeding into an expanding or unconfined haematoma with haemodynamic instability. Relative indications for surgery are massive urinary extravasation and extensive nonviable renal tissue [1435].

Follow-up

In paediatric patients with renal trauma, routine blood pressure checks to diagnose hypertension is recommended in the long-term follow-up, since post-traumatic renal hypertension rate varies between 4.2 and 18%, particularly in cases with concomitant vascular injury [1430, 1436]. However, there is a dearth of long-term data on the risk of developing hypertension in children.

*24.1.5 **Recommendations for the diagnosis and management of paediatric renal trauma***

Recommendations	Strength rating
Use imaging in all children who have sustained a blunt or penetrating trauma, irrespective of the presence of haematuria, particularly when the history reveals a deceleration trauma, direct flank trauma or a fall from a height.	Strong
Use contrast-enhanced computed tomography scanning with delayed images for diagnostic and staging purposes.	Strong
Manage most injured kidneys conservatively.	Strong
Perform angioembolisation or surgical intervention in case of haemodynamic instability or a Grade V renal injury.	Strong

24.2 Paediatric ureteral trauma

Injuries to the ureter are rare. The ureter is well-protected. The upper part is protected by its close proximity to the vertebral column and paraspinal muscles and the lower part by its route through the bony pelvis. In addition, the ureter is a small target, and both flexible and mobile. This also means that ureteral injuries are caused more often by penetrating trauma than blunt trauma [1437]. Since the ureter is the sole conduit for urinary transport between the kidney and the bladder, any ureteral injury can threaten the function of the ipsilateral kidney.

*24.2.1 **Diagnostic evaluation***

As there are no classical clinical symptoms suggestive of ureteral trauma, it is important to carry out a careful diagnostic workup using various imaging modalities. Unfortunately, initial imaging studies, such as IVP and routine CT scans, are unreliable. A study of 11 disruptions of the ureteropelvic junction found that 72% had a normal or nondiagnostic IVP on initial studies [1437]. Diagnostic accuracy of CT scanning can be improved by performing a delayed CT scan up to ten minutes after injection of the contrast material [1438]. The most sensitive diagnostic test is a retrograde pyelogram.

It is not uncommon for patients to present several days after the injury, when the urinoma produces flank and abdominal pain, nausea and fever. Due to symptoms being often vague, it is important to remain suspicious of a potential undiagnosed urinary injury following significant blunt abdominal trauma in a child.

*24.2.2 **Management***

Immediate repair during abdominal exploration is rare. Minimally invasive procedures are the method of choice, especially since many ureteral injuries are diagnosed late after the traumatic event. Percutaneous or nephrostomy tube drainage of urinomas can be successful, as well as internal stenting of ureteral injuries [1439]. If endoscopic management is not possible, primary repair of partial lacerations should be carried out together with internal stenting. The management of complete lacerations, avulsions or crush injuries depends on the amount of ureter lost and their location. If there is an adequate healthy length of ureter, a primary ureteroureterostomy can be performed. If primary reanastomosis is not achievable, distal ureteral injuries can be managed using a psoas bladder hitch, Boari flap or even nephropexy. Proximal injuries can be managed using transureteroureterostomy, autotransplantation or ureteral replacement with bowel or appendix [1440].

*24.2.3 **Recommendations for the diagnosis and management of paediatric ureteral trauma***

Recommendations	Strength rating
Diagnose suspected ureteral injuries by retrograde pyelogram.	Strong
Manage ureteral injuries endoscopically, using internal stenting or drainage of a urinoma, either percutaneously or by means of a nephrostomy tube.	Weak

24.3 Paediatric bladder injuries

The paediatric bladder is less well-protected than the adult bladder, and is therefore more susceptible to injuries, especially when full, due to:

- its higher position in the abdomen and its exposure above the bony pelvis;
- the fact that the abdominal wall provides less muscular protection; and
- the fact that there is less pelvic and abdominal fat surrounding the bladder to cushion it during trauma.

Blunt trauma is the most common cause of significant bladder injury. In adults, bladder injury is often associated with pelvic fractures. This is less common in children, because the paediatric bladder is situated above the pelvic ring. In a large prospective study, only 57% of children with pelvic fractures also had a bladder injury, compared to 89% of adults [1441].

*24.3.1 **Diagnostic evaluation***

The characteristic signs of bladder injury are suprapubic pain and tenderness, an inability to urinate, and visible haematuria (95% of injuries). Patients with a pelvic fracture and visible haematuria present with a bladder rupture in up to 45% of cases [1442].

The diagnosis of bladder rupture can be difficult in some cases. The bladder should be imaged both when fully distended and after drainage using standard radiography or with axial imaging (e.g. CT scan). Optimal imaging results are achieved through retrograde filling of the bladder using a catheter. Despite advances in CT imaging, the bladder must still be filled to capacity to accurately diagnose a possible bladder injury [1443].

Blunt injuries to the bladder are categorised as:

- contusions with damage to the bladder mucosa or muscle, without loss of bladder wall continuity or extravasation; and
- ruptures, which are either intraperitoneal or extraperitoneal.

Intraperitoneal bladder ruptures are more common in children due to the bladder's exposed position and the acute increase in pressure during trauma. These factors cause the bladder to rupture at its weakest point, i.e. at the dome. Extraperitoneal lesions occur in the lower half of the bladder and are almost always associated with pelvic fractures. A cystogram should demonstrate extravasation into the perivesical soft tissue in a typical flame pattern and the contrast material is confined to the pelvis.

*24.3.2 **Management***

Contusions usually present with varying degrees of haematuria and are treated with catheter drainage alone.

24.3.2.a Intraperitoneal injuries

The accepted management of intraperitoneal bladder ruptures is open surgical exploration and primary repair. Postoperative drainage with a suprapubic tube is mandatory. Recent data suggest that transurethral drainage may be equally effective, with fewer complications, resulting in shorter periods of diversion [1444]. Usually, after approximately seven to ten days, a repeat cystogram is performed to ensure adequate healing.

24.3.2.b Extraperitoneal injuries

Nonoperative, supportive management with catheter drainage for seven to ten days is the method of choice for extraperitoneal bladder rupture. However, if there are bone fragments within the bladder, these must be removed and the bladder must then be repaired and drained according to the principles for treating intraperitoneal ruptures [1445].

*24.3.3 **Recommendations for the diagnosis and management of paediatric bladder injuries***

Recommendations	Strength rating
Use retrograde cystography to diagnose suspected bladder injuries.	Strong
Ensure that the bladder has been filled to its full capacity and an additional film is taken after drainage.	Strong
Manage extraperitoneal bladder ruptures conservatively with a transurethral catheter left in place for seven to ten days.	Strong
Perform surgical exploration in cases of intraperitoneal bladder ruptures.	Strong

24.4 Paediatric urethral injuries

Except for the penile part of the urethra, the paediatric urethra is quite well-protected. In addition, the shape and elasticity of the paediatric urethra mean that the urethra is seldom injured by trauma. However, a urethral injury should be suspected in any patient with a pelvic fracture or significant trauma to the perineum until confirmed, otherwise by means of a diagnostic workup.

*24.4.1 **Diagnostic evaluation***

Patients with suspected urethral trauma and pelvic fractures usually present with a history of severe trauma, often involving other organ systems.

Signs of urethral injury include blood at the meatus, visible haematuria, pain during voiding or an inability to void. There may also be perineal swelling and haematoma involving the scrotum. A rectal examination to determine the position and fixation of the prostate is important in any male with a suspected urethral injury. The prostate (although small), as well as the bladder, may be displaced up out of the pelvis, especially in membranous urethral trauma.

Radiographic evaluation of the urethra requires a retrograde urethrogram. It is important to expose the entire urethral length, including the bladder neck. If a catheter has already been placed and, if urethral trauma is suspected, the catheter should not be removed. Instead, a small infant catheter can be placed into the distal urethra along the catheter to allow the injection of contrast material for a diagnostic scan [1446].

24.4.2 ***Disease management***

As these patients may be unstable due to the nature of their injuries, the urologist's initial responsibility is to provide a method of draining and monitoring urine output.

A transurethral catheter should only be inserted if there is a history of voiding after the traumatic event, and if a rectal and pelvic examination, as described above, has not suggested a urethral rupture. If the catheter does not pass easily, an immediate retrograde urethrogram should be performed. A suprapubic tube can be placed in the emergency department percutaneously, or even in the operating room if the patient must undergo immediate exploration due to other life-threatening injuries.

There are often no associated injuries with a bulbar urethral or straddle injury, and management is therefore usually straightforward. In these cases, a transurethral catheter is the best option for preventing urethral bleeding and/or painful voiding [1447].

The initial management of posterior urethral injuries remains controversial, mainly regarding the long-term results with primary realignment compared to simple suprapubic drainage with later reconstruction.
The main goals in the surgical repair of posterior urethral injuries are:

- providing a stricture-free urethra; and
- avoiding the complications of urinary incontinence and erectile dysfunction.

Anterior urethral injury

The data for anterior urethral injury repair is much the same as for adults. Small lacerations can be repaired by simple closure. Complete ruptures without extensive tissue loss are treated with anastomotic repair [1448]. Penetrating injuries require peri- and postoperative antibiotic treatment [1449].

Immediate urethroplasty is generally performed in blunt injuries. The long-term outcomes (patency rate, potency rate) of adult patients treated with immediate urethroplasty are similar to those initially treated with suprapubic diversion and delayed urethroplasty [1450]. The main advantage of performing immediate urethroplasty is that this strategy significantly reduces the time to spontaneous voiding from two to six months to three weeks on average. Spongiosal contusion and haematoma during immediate urethroplasty will make the operation technically more demanding. Therefore, immediate urethroplasty should be performed by a dedicated urethral surgeon [1451].

Posterior urethral injury

Unlike anterior urethral injuries with immediate realignment, in children with posterior urethral injuries, a staged approach with delayed repair may be more appropriate.

In children, there is significantly less experience with delayed repair, with a large paediatric series of delayed repair in 68 boys reporting successful voiding and a continence rate of 90% [1452]. Another study reported strictures and erectile dysfunction in 67% of boys, although all the boys were continent postoperatively [1247]. A follow-up study on 15 patients who underwent delayed urethroplasty for blunt urethral trauma during childhood reported high long-term success rates, with a low rate of long-term urinary and sexual dysfunction in adulthood [1453].

Revision surgery

A large study of revision urethroplasty analysing revision urethroplasty following pelvic floor urethral injuries in children and adolescents demonstrated that these injuries appeared to be more common in the developing world, with more complex findings and longer gaps. In support of the above findings, these patients were best managed with delayed transperineal repair with self-reported success of up to 85% [1454]. On the other hand, a small prospective study demonstrated good results with immediate primary endoscopic realignment in patients with posterior urethral and bladder neck injuries [1455]. This may serve as an alternative to those with permitting endoscopic anatomy post-injury. A large study exploring outcomes of various urethroplasty techniques in both boys and girls demonstrated that most paediatric pelvic floor urethral injuries can be addressed through a transperineal approach with reasonable long-term outcomes (>80%), however, up to 25% of patients require further endoscopic/open procedures during follow-up. In challenging cases, salvage procedures utilising vascular-based flaps as a urethral substitute can yield good results. The numbers lost to follow-up, however, were significant at 40.6% [1456].

In a study of 18 boys undergoing urethroplasty for strictures (traumatic/iatrogenic), post-void dribbling and urgency were the main patient-reported outcome measures (PROMs) following surgery, with universally high satisfaction rates. Patient-reported outcome measures are an important consideration for urologists performing

these procedures on children, because they will likely need continued long-term follow-up [1457]. In those who have previously experienced a failed urethroplasty following pelvic fracture-associated urethral injuries, most cases of recurrent posterior urethral strictures of <3cm in length can be treated with a perineal urethroplasty with reasonable success rates. Complex and long-segment (higher than 3cm) strictures require use of ancillary procedures such as transpubic urethroplasty, substitution urethroplasty and Mitrofanoff appendicovescostomy with complication rates in adolescents of 33% [1458].

*24.4.3 **Recommendations for the diagnosis and management of paediatric trauma***

Recommendations	Strength rating
Assess the urethra by means of retrograde urethrogram in case of suspected urethral injury.	Strong
Perform a rectal examination to determine the position of the prostate.	Strong
Manage urethral injuries conservatively initially if a transurethral catheter can be placed.	Strong
Manage posterior urethral injuries by means of either: • primary drainage with a suprapubic catheter alone and delayed repair; or • primary realignment with a transurethral catheter.	Weak

24.5 Urosepsis

Refer to Chapter 12 on urinary tract infections in children.

25. PERIOPERATIVE MANAGEMENT

25.1 Preoperative fasting, intraoperative fluid therapy, postoperative feeding, fasting and fluid management

*25.1.1 **Epidemiology, aetiology and pathophysiology***

Children have a different total body fluid distribution, renal physiology and electrolyte requirements, as well as weaker cardiovascular compensation mechanisms compared to adults [1459]. During development, children have a high metabolic rate and lower fat and nutrient stores, which means they are more susceptible to metabolic disturbances caused by surgical stress [1460]. The metabolic response to anaesthesia and surgery in infants and children is related to the severity of the operation [1461].

*25.1.2 **Disease management***

25.1.2.a Preoperative fasting

Preoperative fasting has been advocated for elective surgery to avoid the complications associated with pulmonary aspiration during induction of anaesthesia. New regimens include a one-hour limitation for clear liquids [1462, 1463] without increased risk of pulmonary aspiration [1464]. Several studies have shown that fasting times in clinical practice often exceed the Guidelines with average fasting times of six to ten hours [1463-1465]. Compared to adults, children have a higher metabolic rate and low glycogen stores and impaired gluconeogenesis, which makes hypoglycaemia an important issue to consider, especially in children <36 months old [1463]. Therefore, it is important to prevent extended fasting times. Clear-liquid carbohydrate drinks have been proposed to reduce these fasting times [1466]. The presence of Type I diabetes does not necessitate different fasting instructions from those for healthy children [1467]. Depending on the length and scale of the procedure, special attention to appropriate insulin administration, management of hypo- and hyperglycaemia, as well as other metabolic abnormalities, is required [1468].

Table 12 provides the current guidelines for preoperative fasting for elective surgery [1467].

Table 12: Preoperative fasting times for elective surgery

Ingested material	Minimum fasting period (hours)
Clear liquids	1
Breast milk	3
Formula milk-based products	4
Light meal	6

25.1.2.b Maintenance therapy and intraoperative fluid therapy

The goal of intraoperative fluid management is to sustain homeostasis by providing the appropriate amount of parenteral fluid. This maintains adequate intravascular volume, cardiac output, and oxygen delivery to tissues at a time when normal physiological functions have been altered by surgical stress and anaesthetic agents.

The main goal of intraoperative fluid management is to maintain a normal extracellular fluid volume (EFV). During the intraoperative period, fluid deficits may be induced by preoperative fasting, blood loss or third-space losses.

25.1.2.c Postoperative feeding, fasting and fluid management

Checking serum chemistry after uncomplicated surgery is not mandatory in children with normal preoperative renal and hepatic function. However, if oral intake has been postponed for >24 hours (e.g. as in intestinal surgery), there is an increased risk of electrolyte abnormalities, requiring further assessment and subsequent management, particularly with potassium. Postoperative findings, such as decreased bowel movements and ileus, may be signs of hypokalaemia.

Children who undergo interventions to relieve any kind of obstructive diseases deserve particular attention, especially due to the risk of polyuria as a result of post-obstructive diuresis [1469]. In children who develop polyuria, it is important to monitor fluid intake and urine output, as well as renal function and serum electrolytes. If necessary, clinicians should not hesitate in consulting with a paediatric nephrologist.

In children who have undergone nonabdominal surgery, studies have suggested that gastric motility returns to normal one hour after emergence from anaesthesia [1470]. Early postoperative intake of fluid in children who have undergone minor or nonabdominal urological surgery is associated with reduced postoperative vomiting and lower opioid use [1471] and is therefore encouraged.

Intraperitoneal surgery and the use of bowel may lead to decreased bowel motility in the postoperative period, which can lead to paralytic ileus. Experimental and clinical studies have shown that traditional restriction of oral intake after abdominal surgery has no basis in scientific evidence and adverse effect on tissue regeneration and enzymatic function has been reported. Due to those deleterious effects of fasting, early enteral nutrition is preferred to parenteral nutrition [1472]. In newborns, early intragastric, small-volume breast is well tolerated in the postoperative period and seems to provide a trophic effect on gut mucosa [1472].

Chewing gum is a type of sham feeding that promotes intestinal motility by means of cephalic-vagal stimulation. Chewing gum is usually well-tolerated and accepted by older children without any contraindication. Although the evidence is limited, it can potentially enhance bowel recovery in the postoperative period in children [1473].

The ERAS protocol is a patient-centred, multimodal approach to optimise postoperative recovery. This protocol includes pre- and intraoperative element, such as minimal preoperative fasting and careful intraoperative fluid management and focuses on postoperative care. The postoperative ERAS protocol suggests starting clear fluid intake on the evening of surgery and a normal diet the day after surgery and thereby early discontinuation of IV fluids. Further focus is on early mobilisation, preventing epidurals and omitting or early removal of external tubes [1474].

The implementation of an ERAS protocol has resulted in a shorter length of hospital stays, faster bowel recovery and reduced need for postoperative, opioid-free administration [1474, 1475]. The implementation of ERAS protocols does not seem to result in higher complication and readmission rates. Instead, some studies have even demonstrated a significant reduction in complication occurrence [1474]. When implementing ERAS in children with neurological abnormalities, special attention should be given to bowel management, with preoperative treatment of constipation and early postoperative continuation of routine bowel management.

25.1.3 Summary of evidence and recommendations for the management of perioperative fluid management

Summary of evidence	LE
The current evidence recommends reducing clear fluid fasting to one hour, reducing breast milk fasting to three hours, reducing formula milk-based products to four hours and allowing a light meal six hours before anaesthesia induction for elective procedures.	1
Following abdominal surgery, ERAS protocols can be used to reduce recovery times and complications.	1

Recommendations	Strength rating
Ensure shorter preoperative fasting periods for elective surgeries (one hour for clear liquids, three hours for breast milk, four hours for formula milk-based products and six hours for a light meal).	Strong
Start early postoperative oral fluid intake in all patients scheduled for minor surgical procedures.	Strong
Use enhanced recovery after surgery protocols for abdominal surgery in children with pre-existing normal bowel function.	Strong

25.2 Postoperative pain management: general information

*25.2.1 **Epidemiology, aetiology and pathophysiology***

The provision of adequate pain control requires proper pain evaluation, accurate choice of drug and route of administration, as well as consideration of age, physical condition and type of surgery and anaesthesia [1476].

*25.2.2 **Diagnostic evaluation***

Assessment of pain is the first step in pain management. Several pain assessment tools have been validated according to the child's age, cultural background, mental status, communication skills and physiological reactions [1477]. Depending on the child's age, the 0-10 numeric rating scale; Faces Pain Scale - Revised (FPS-R); Face Legs Activity, Cry and Consolability (FLACC) scale; or Colour Analog Scale (CAS) can be used [1478]. One of the most important topics in paediatric pain management is informing and involving the child and caregivers during this process. Patient and family-controlled analgesia is the preferred pain management in the hospital and at home if the child and caregivers are provided with the correct information [1479, 1480].

*25.2.3 **Disease management***

25.2.3.a Drugs and route of administration

Pre-emptive analgesia is an important concept that aims to induce the suppression of pain before neural hypersensitisation occurs [1481]. Regional anaesthesia is given intraoperatively, which can include a regional nerve block or local wound infiltration and has proven to reduce the need for postoperative analgesia [412]. The WHO's 'pain ladder' is a useful tool for the pain management strategy [1482]. Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are the first choice. As they become insufficient to prevent pain, weak and strong opioids are added to oral drugs to achieve balanced analgesia. A proposed strategy for postoperative analgesia may be as follows:

1. intraoperative regional block and/or local wound infiltration;
2. paracetamol + NSAID;
3. paracetamol + NSAID + weak opioid (e.g. tramadol or codeine); and
4. paracetamol + NSAID + strong opioid (e.g. morphine, fentanyl, oxycodone or pethidine).

The use of opioids in children has long held a standard role in the postoperative management of pain. Increased recognition of the adverse effects of opioids and prolonged opioid dependency demand a balanced intraoperative administration of opioids [1483]. Intraoperative adequate dosage of paracetamol and NSAIDs results in a decrease in opioid requirement in children [1484, 1485].

25.2.3.b Circumcision

Circumcision requires anaesthesia and proper pain management [1486]. Potential analgesic interventions during circumcision include the use of a dorsal penile nerve block (DPNB) or ring block, topical anaesthetics (depending on age, weight and body surface), and sucrose, preferably in combination [412, 1487]. Caudal blockade methods have similar efficacy compared to DPNB [1488]. However, caregivers should be informed about the more-frequent incidence of postoperative motor weakness and micturition problems [1487, 1488].

25.2.3.c Penile, inguinal and scrotal surgery

Caudal blocks and peripheral nerve blocks (DPNB and pudendal) are commonly used methods for analgesia in hypospadias surgery. Several agents with various doses, concentrations and administration techniques have been used. All have been shown to have adequate postoperative analgesic properties, and no increase in postoperative complications was seen [411-413]. Severe bladder spasms caused by the presence of the bladder catheter can be managed with antimuscarinic medications.

For inguinoscrotal surgery, various regional anaesthesia methods have been investigated, such as transversus abdominis plane block, quadratus lumborum nerve block, ilioinguinal/iliohypogastric nerve blocks and caudal blocks. All of these methods have been shown to have adequate postoperative analgesic properties [1489]. In

addition, local anaesthetics such as clonidine or dexmedetomidine have been shown to prolong the analgesic effect [1490, 1491].

25.2.3.d Bladder and kidney surgery

Continuous local infusion (pain catheter) has been shown to be effective and reduces the need for postoperative opioids [1492-1494], as well as systemic (intravenous) application of analgesics [1495]. Ketorolac (NSAID) is an effective agent that decreases the frequency and severity of bladder spasms, the length of postoperative hospital stay and costs, and intraoperative opioid administration [1496]. Open kidney surgery is particularly painful, because all three muscle layers are cut during conventional flank incision. A dorsal lumbotomy incision may be a good alternative in small children because of the shorter postoperative hospital stay and earlier return to oral intake and unrestricted daily activity [1497]. Caudal and paravertebral blocks continuous epidural analgesia, as well as rectus sheath and transversus abdominis plane blocks, have been shown to decrease post-operative morphine requirement after abdominal and renal surgery [1498-1500].

25.2.4 Summary of evidence and recommendations for the management of post-operative pain

Summary of evidence	LE
The use of adequate paracetamol and NSAIDs reduces opioid need postoperatively.	1

Recommendations	Strength rating
Prevent/treat pain in children of all ages.	Strong
Evaluate pain using age-compatible assessment tools.	Strong
Use pre-emptive and balanced analgesia to decrease the need for opioids.	Strong

25.3 Antibiotics management: general information

It is well established that perioperative antibiotics prevent infections following surgery, but limited data are available for antibiotic management in paediatric genitourinary procedures. Antibiotic prophylaxis carried the risk of developing drug-resistant bacteria and adverse effects such as allergic reactions. Moreover, in childhood, some antibiotics are not recommended, and their use is discouraged except for in severe cases.

In 2020 Snyder *et al.* conducted one of the first systematic reviews on perioperative antibiotic practices in the paediatric urology literature [1501]. They reported that the majority of the articles did not provide accurate information on perioperative antibiotic practices. Other studies demonstrated wide variations in practice patterns for antibiotic usage among paediatric urologists [407, 1502].

Perioperative prophylactic antibiotics in hypospadias repair have been widely debated in the literature. A meta-analysis demonstrated a high risk of bias and a low level of evidence in terms of postoperative prophylactic antibiotics preventing complications following hypospadias repair [410]. On the contrary, a consensus exists for no perioperative antibiotics following circumcision [1501].

A prospective, randomised, controlled, non-blinded, non-placebo study was performed on the effectiveness of continuous antibiotic prophylaxis in patients with JJ stents, with a total of 105 patients. They concluded that continuous antibiotic prophylaxis reduced the incidence of febrile UTIs, particularly in children with a history of febrile UTI and LUTS [1503].

There is a need for standardisation of perioperative antibiotic usage for paediatric urological operations. However, a lack of prospective studies and RCT's are the main barriers for creating evidence-based guidelines on this particular topic.

25.4 Thromboprophylaxis management: general information

Thromboprophylaxis in children involves preventive measures aimed at reducing the risk of blood clot formation. Unlike adults, most children do not require thromboprophylaxis after surgery. It is only considered in certain high-risk situations such as underlying medical conditions like malignancies, congenital heart disease and so on. Moreover, very limited data are available on the safety and efficacy of anticoagulants in paediatric practice.

25.4.1 ***Epidemiology, aetiology, pathophysiology***

The incidence of venous thromboembolism (VTE) in children is low but has increased due to an increased use of central venous catheters (CVL) and an improvement in detection [1504]. Some authors suggest an incidence of five to eight cases of symptomatic VTE per 10,000 hospital admissions (0.05%-0.08%), but the true incidence may be higher as the majority of VTEs are clinically silent in children [1505]. In infants, VTE is most often associated with sepsis, congenital haematological disorders and malignancies. At adolescence, the physiology of the coagulation system matures and additional risk factors such as smoking, obesity, pregnancy and oestrogen-containing oral contraceptives become relevant. There is a 2:1 preponderance of females among adolescents who develop VTE.

The risk of VTE after urological surgery has been shown to have an incidence of 0.12%, which increases to 0.2% for prolonged hospitalisation [1506, 1507].

Before adolescence, the absolute risk of VTE following major surgery, trauma, or immobilisation is low, even in children who have thrombophilia [1508]. Therefore, thromboprophylaxis is not recommended.

The risk of developing VTE should focus on adolescents (> 13 years) particularly those with one or more risk factors, such as those mentioned above [1509].

General preventive measures are fundamental to prevent VTE and should include: adequate peri- and postoperative hydration, early mobilisation after surgery and removal of CVLs as soon as possible. In post-pubertal girls undergoing any kind of surgery, consideration should be given to withholding the combined contraceptive pill for four weeks prior to planned surgery, particularly if there is a strong family history of thrombosis or a known thrombophilic risk factor [1505].

25.4.2 ***Diagnostic evaluation***

Identifying thrombophilic risk factors in the family and patient history is important. Symptoms are similar to adult patients with pain, oedema of the dependent areas and development of collateral vessel circulation. However, children with VTE also have some unique presentations, such as *purpura fulminans*. As with adults, the diagnosis of VTE in the upper venous system is confirmed using doppler US and, if necessary, with venography. However, the optimal diagnostic test for lower limb VTE and pulmonary embolism in children is undefined at the present time, but US is the first approach [1510].

25.4.3 ***Disease management***

The aims of antithrombotic therapy in children are similar to those for adults with VTE. Management of childhood VTE is often complex, due to the frequent coexistence of medical and surgical diseases, and the fact that limited data is available on the efficacy and safety of these drugs in paediatric practice. A multidisciplinary management approach should be sought.

Medical device and physiological mechanism for thromboprophylaxis

Physical treatments for thromboprophylaxis are the same used for adult patients: graduated compression stockings (GCS), intermittent pneumatic compression (IPC) devices and venous foot-pumps (VFPs). No paediatric sizes of GCS or IPC are yet available, therefore, they are applicable only to older patients - usually those over 40kg in weight or older than thirteen years. Intermittent pneumatic compression devices have been used for intraoperative use in children aged thirteen years and over who weigh >40kg and who are expected to undergo prolonged surgery [1505, 1509].

The evidence for the use of these devices is significantly less than for anticoagulant options and few data are available in children and adolescents [1511]. These devices should be combined with pharmacological prophylaxis. Early mobilisation and good hydration should be encouraged in patients of all ages.

25.4.4 ***Pharmacological treatment for thromboprophylaxis***

The use of anticoagulant agents to prevent VTE is very limited in children. None of the preparations are licensed in the paediatric age group. Low molecular weight heparins (LMWHs) have become the mainstay anticoagulant in the paediatric population, both for prophylaxis and treatment due to the more predictable pharmacokinetics compared with unfractionated heparin. Low molecular weight heparins allow less-frequent monitoring and have a lower incidence of serious side effects. Compared with adult patients, children require higher doses of LMWH, which decrease with age due to a decreased thrombin production and a high renal clearance. The most commonly used drugs are enoxaparin and dalteparin, and the major bleeding rate for prophylactic use of LMWH is low [1505, 1509, 1512].

Children older than 13 years with multiple risk factors for thrombosis should be considered for thromboprophylaxis with LMWH, particularly if immobilisation for more than 48 hours is expected [1512].

*25.4.5 **Prevention of CVL-related VTE***

The presence of a CVL is the most significant risk factor for VTE in children. Central venous catheters placed in the right internal jugular seem to be associated with a lower risk of VTE. There is also evidence that femoral CVLs are associated with a particularly high risk for thrombosis in children [1505].

Thromboprophylaxis did not prevent CVL-related VTE both in prospective studies and RCTs, because most of these thrombi were transient and resolved spontaneously without therapy [1513].

*25.4.6 **Summary of evidence and recommendations for the management of thromboprophylaxis management***

Summary of evidence	LE
The incidence of perioperative thromboembolic events in the paediatric population is generally very low.	1
Patients >13 years of age with additional risk factors should be considered for venous thromboembolism prophylaxis.	1
Standard antithrombotic prophylaxis is not recommended, due to a lack of high quality RCTs and accepted guidelines concerning perioperative thromboprophylaxis in children.	4

Recommendations	Strength rating
Use physical methods for venous thromboembolism prophylaxis (VTE) risk reduction in older children and adolescents who are at increased risk of VTE.	Strong
Consider low molecular weight heparin VTE prophylaxis in children, particularly adolescents, with additional risk factors.	Strong

25.5 Premedication management: general information

Most children undergoing anaesthesia and surgery develop anxiety that could lead to adverse reactions. Many factors may influence preoperative anxiety [1514]. Anxiety and distress can be prevented or relieved, combining premedication, distraction techniques and parental or caregivers' presence. Nonpharmacological, age-appropriate methods, such as play therapy, toys, storybooks, videos, tablet and mobile phone can all be useful. A successful plan must therefore take into account the age and temperament of the child [1515].

The most important goal of premedication is to alleviate patients' anxiety and facilitate a smooth separation of the child from their parents/caregivers. Preanaesthetic sedatives in children must be given in a timely fashion preoperatively, and include midazolam, clonidine, ketamine and dexmedetomidine, but no consensus has been reached on the best choice against preoperative anxiety. Clinicians should select the appropriate premedication depending on the patient's age, disease and psychological status [1516].

Topical anaesthesia should be used to reduce or eliminate the pain and anxiety of an intravenous access placement when an intravenous induction is required. The most commonly used local anaesthetic creams require 20 to 60 minutes for maximal effect, but they can cause vasoconstriction that could make the vein harder to see and cannulate [1514, 1516].

*25.5.1 **Recommendations for premedication management: general recommendations***

Recommendations	Strength rating
Use nonpharmacological, age-appropriate premedication methods to decrease anxiety levels in children before surgery.	Weak
Use pharmacological premedication to decrease anxiety levels in children and monitor for potential side effects.	Strong

26. BASIC PRINCIPLES OF LAPAROSCOPIC SURGERY IN CHILDREN

26.1 Epidemiology, aetiology and pathophysiology

The use of laparoscopy and robot-assisted laparoscopic surgery is rapidly increasing and has gained widespread acceptance for many urological surgeries in children [1517]. Laparoscopy is commonly performed for nonpalpable testis, nephrectomy, heminephrectomy, varicocelectomy, pyeloplasty and ureteral reimplantation. This expanding scope related to technological advancements allows surgeons to perform more-complex procedures in a minimally invasive fashion even in infants and younger children. Generally, well-established benefits of minimally invasive surgery are decreased pain, shorter convalescence and better cosmetics compared to traditional open surgery [837, 1518]. When comparing the transperitoneal and retroperitoneal approach, there was no difference in recovery of bowel function [1519]. Additional advantages of robotic surgery over conventional laparoscopy include ergonomics, 3D vision, better manoeuvrability, decreased tremor and easy learning curve. Limitations to be considered are increased operative time, smaller working space at a young age, cost, and experience of the surgeon and anaesthesiologist. While the success and complication rates are comparable for nephrectomy and pyeloplasty, advantages of laparoscopy and robotic surgery for ureteral reimplantation have not been proven and this can only be recommended for experienced centres.

As worldwide experience increases, there is an accumulating awareness about the physiological consequences related to intra- and retroperitoneal CO_2 insufflation in children. In contrast to traditional open surgery, pneumoperitoneum may have physiological responses which require close monitoring during surgery and should be taken seriously.

26.2 Technical considerations and physiological consequences

*26.2.1 **Preoperative evaluation***

Laparoscopy in children requires specific anaesthetic precautions. Physiological effects of CO_2 pneumoperitoneum, positioning of the patient, and potentially increased operative time must be considered by the anaesthesiology team. Therefore, a detailed medical examination and risk assessment is mandatory pre-operatively. Especially, the cardiac and pulmonary systems should be assessed, as increased intra-abdominal pressure may lead to decreased ventricular preload [1520].

*26.2.2 **Abdominal insufflation***

Abdominal insufflation is the main principle of laparoscopic surgery to create working space for the surgeon. Carbon dioxide is most commonly used for insufflation in laparoscopic centres throughout the world. Other alternatives reported are nitrous oxide, helium, argon and air. However, CO_2 is considered to be the best available gas, as it is colourless, cheap, has high solubility in the vascular system [1521] and is excreted by the pulmonary system, making it the safest option. Smaller children and infants absorb more CO_2 than older children [1522], suggesting the need for more attention both during and soon after laparoscopic surgery for these children.

Most complications of laparoscopy are attributable to gaining access to the abdominal cavity. One study reporting complications of >5,400 paediatric laparoscopic surgeries showed that there was an overall complication rate of 5.3%, of which 4.2% were related to problematic insufflation (subcutaneous emphysema, gas embolism, injury to the organs and vascular structures, mis-insufflation and so on) [1523]. There are two main and well-established techniques for initial access to the abdomen or retroperitoneum: open technique (Hasson) and Veress needle. Studies comparing these two different access techniques in paediatric laparoscopic urological procedures showed similar complication rates [1524]. The vast majority of the complications were minor and related to lack of surgical experience. Particularly in infants and smaller children, the Panel recommends the open access technique to reduce the chance of complications.

Elasticity of the abdominal wall is age-related and is higher in infants and small children compared to older children [1525].

Pneumoperitoneal pressure (PnP in mmHg) is one of the critical points that laparoscopic surgeons must considered carefully. An RCT compared two different pneumoperitoneal pressure groups (6-8mmHg vs. 9-10mmHg) in infants weighing less than 10kg [1526]. The results of the RCT demonstrated that higher pressures were associated with more pronounced respiratory and haemodynamic changes, as well as increased postoperative pain scores and prolonged time to resume feeding.

26.2.3 ***Pulmonary effects***

After intra-abdominal insufflation, the diaphragm is pushed upwards due to increased abdominal pressure. This leads to decreased total pulmonary compliance. Combined with CO_2 absorption, this may lead to hypercarbia and acidosis, particularly in case of prolonged operative time or low pulmonary reserve such as in infants. Trendelenburg position may also aggravate the situation in operations in the pelvic region, such as antireflux or bladder neck surgeries. Several studies revealed increased end tidal CO_2 (ET CO_2) related to CO_2 absorption [1522, 1527, 1528]. One study showed a 33% increase in ET CO_2 in the majority of neonatal laparoscopic and thoracoscopic procedures [1529]. Shorter operative time and lower intra-abdominal pressures decrease the risk of increased ET CO_2. Hypoxemia is rarely seen, even in neonates, and can easily be adjusted by increasing minute ventilation. These findings highlight the importance of close monitoring of the children.

26.2.4 ***Cardiovascular effects***

Intra-abdominal pressure, CO_2 absorption and positioning may also affect the cardiovascular system. It has been shown in adults that, after initiation of pneumoperitoneum, cardiac output and stroke volume decrease, while mean arterial pressure, central venous pressure and systemic vascular resistance increase [1530]. Similar outcomes have been reported during paediatric laparoscopy with some nuances. Cardiac output was 30% decreased while blood pressure remained stable during laparoscopic orchidopexy with PnP of 10mmHg in children between the ages of 6-30 months [1531]. When PnP was lowered from 12mmHg to 6mmHg, cardiac index and other vascular parameters normalised [1532]. Using high intra-abdominal pressures in infants with congenital cardiac abnormalities may result in reopening of cardiac shunts such as the foramen ovale and ductus arteriosus [1533]. Although cardiovascular effects of using high PnP are clinically measurable, they may not have a significant clinical impact on healthy children. However, it is clear that using lower pressures is safer, particularly in smaller children.

26.2.5 ***Effects on renal function***

A study measuring renal oxygenation with near-infrared spectroscopy (NIRS) during laparoscopy showed that pneumoperitoneum might have a negative effect on renal oxygenation [1534]. However, this effect was reversible after desufflation. Other studies showed that pneumoperitoneum may also have adverse effects on renal blood flow [1535]. High intra-abdominal pressures and reverse Trendelenburg position may cause decreased glomerular filtration rate and decreased urine output. One study has shown that 88% of infants and 14% of children above the age of one year old develop anuria within 45 minutes after initiation of PnP with 8mmHg [1536]. However, urine output recovers with temporary polyuria after the operation. Although the clinical relevance of decreased urine output seems insignificant, it is important to monitor the fluid and electrolyte balance of the children during and after laparoscopic surgery.

26.2.6 ***Effects on neurological system***

Another effect of pneumoperitoneum is increased intracranial pressure (ICP), which normalises after desufflation of the abdomen [1537]. Trendelenburg position, high PnP and hypoventilation are additional risk factors for increased ICP. Laparoscopy is therefore contraindicated in patients with intracranial space occupying lesions [1538]. Children with ventriculoperitoneal shunts require precautions with regards to shunt drainage, however, laparoscopy is not contraindicated [1539].

26.2.7 ***Comparison of robot-assisted laparoscopic surgery versus laparoscopic surgery***

No physiological differences are expected between the two approaches, since pneumoperitoneum must be achieved in the same manner. However, a systematic review comparing robot-assisted laparoscopic pyeloplasty to conventional laparoscopy in infants and children showed no differences in terms of operative success and redo rates between the two techniques [1540]. As for operative time, length of hospital stay and complication rates, the robotic approach appears to be slightly superior in children [1541, 1542]. However, in the infant population, operative time was longer in the robot-assisted approach as compared to conventional laparoscopy, and there was a higher complication rate, mainly due to a higher rate of port-site hernias [1543]. The robot-assisted approach might aid in filling the gap to minimally invasive surgery for paediatric urologists, as it has a shorter learning curve and does not necessarily require prior laparoscopic experience. Downsides to the robotic approach are the size of the instruments, accessibility and costs [1540, 1542].

26.3 Summary of evidence and recommendations for laparoscopy in children

Summary of evidence
Laparoscopy and robotic-assisted laparoscopic surgery can safely be performed in children.
The general benefits of laparoscopy are decreased pain, shorter convalescence and better cosmetics compared to traditional open surgery.
Limitations to be considered are increased operative time, smaller working space with young age, cost, surgeon and anaesthesiologist experience.
Pneumoperitoneum may have physiological effects that require close monitoring during surgery and should be taken seriously.

Recommendations	Strength rating
Use lower intra-abdominal pressure (6-8mmHg) during laparoscopic surgery in infants and smaller children.	Strong
Use open access for laparoscopy in infants and smaller children.	Strong
Monitor for laparoscopy-related cardiac, pulmonary and diuretic responses.	Strong

27. TRANSITIONAL UROLOGY

27.1 Introduction

Transition in urology is defined as the process where an adolescent or young adult with a congenital or acquired urogenital anomaly transitions into adult services and begins to assume increasing responsibility for their own health care, thus becoming the primary decision-maker in their own care. The main goal of the transition process in urology is to preserve renal function, to optimise QoL by achieving and maintaining continence, to treat and manage issues related to sexuality and infertility, and to monitor for progression of the disease process or complications related to interventions [1544-1546].

27.2 Barriers in transition

The process of transition is different for each individual. It is dependent on a complex interplay of factors such as psychosocial development, the onset of puberty, and the persistence and severity of physical and congenital disabilities. The child, caregivers and urologists often have different views and expectations during transition, which can lead to inherent difficulties with noncompliance and failure of attendance. Adolescents expect to be more like their peers without disabilities and experience changes due to puberty, including the willingness to participate in health care agreements. Concurrently, paediatric urologists may opt to increase the number of visits to enable a smoother transition to the adult urologist, without any significant outstanding therapeutic issues. Caregivers may be reluctant to be discharged by the paediatric urologist with whom they had a long-standing relationship.

Finding an adult urologist with expertise in functional and reconstruction urology and with knowledge of both underlying congenital conditions and their optimal treatment can be challenging. The adult urologist must be focused on the overall care of the patient and be able to work in a multidisciplinary team to fill in the gaps of each individual discipline. Strong lines of communication between the relevant specialists are essential (e.g. nephrology, neurosurgery, gynaecology, rehabilitation doctors, orthopaedics) [1544-1547]. Specific key features have been identified that can pose difficulties in the transition process (Table 13).

Table 13: Key structural differences between paediatric and adult care that can pose difficulties in the transition process (adapted from Claeys *et al.*, 2021 [1546])

Feature	Paediatric care	Adult care
Patient management	Involvement of a large multidisciplinary team, often lead by a single provider (referrals within the team)	Smaller teams with subspecialty expertise (referrals to other specialties as needed)
Care approach	Family centred	Patient centred
Patient functioning	Limited independence	Expected independence
Clinic management	Time allotted for detailed discussion with intensive coordination	Usually, shorter appointment times and focused care coordination
Access to psychology	Good access	Often limited access
Follow-up	Regular active follow-up	More passive follow-up

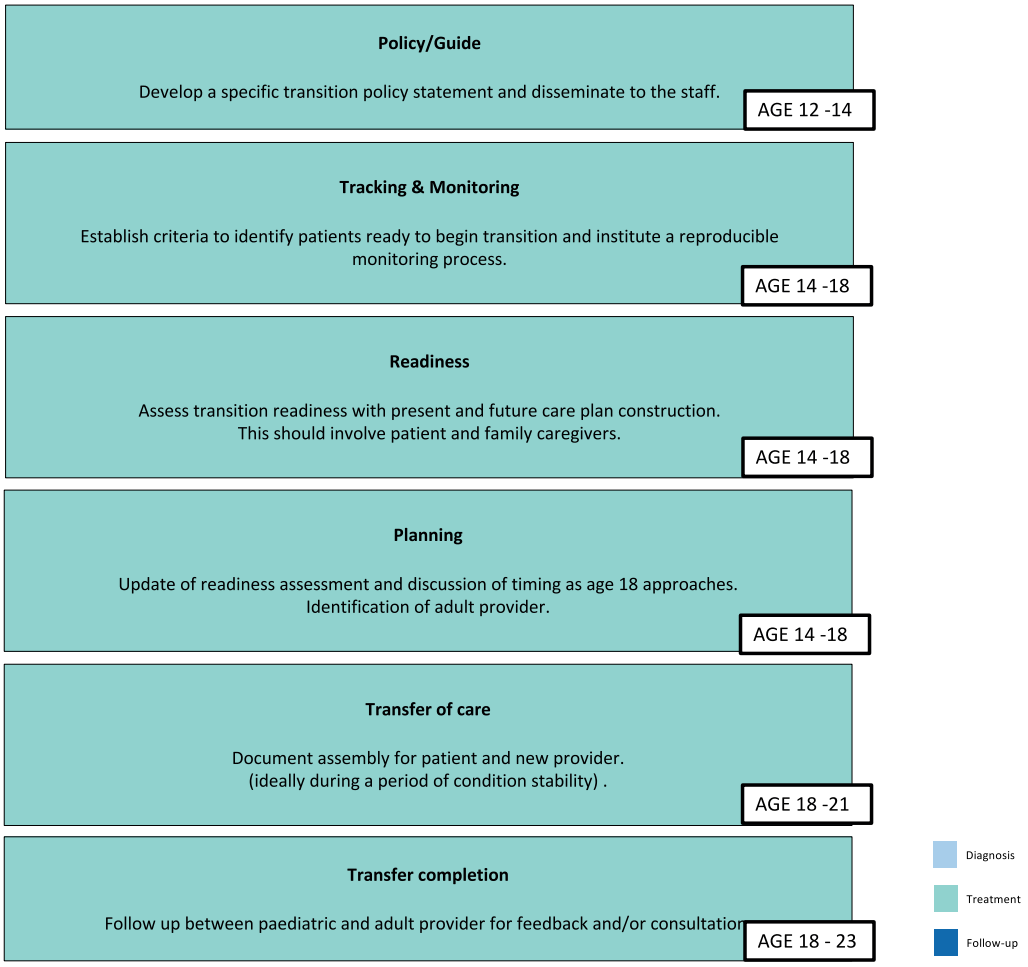
27.3 The transition process

The optimal age at which patients should transition into the care of adult providers has not been firmly established and may need to be individualised to the patient based on their unique situation. Overall, it is important to address transitional care from the age of 12 years, and by 16 years at the latest. A gradual introduction of the adult urologist into the health care team, several years before targeted time of transition, may facilitate the process of transition, as the child and the caregivers gain trust in the new provider [1548].

Early childhood transition planning should focus on developing long-term goals and expectations to promote optimal health and independence, lifelong care access, and financial planning. During the adolescent years, transition preparation should include developing a care plan, decision-making support, supporting self-management development, and addressing care coordination [1549].

Various models of a transition programs have been proposed. Although no single approach has been demonstrated as superior [1550]. The National Alliance to Advance Adolescent Health (https://www.gottransition.org/six-core-elements) has identified six core elements to support transitional care across specialties. For each element, several measures are proposed to allow for a successful transition to adult care. An ideal age for completion of each step is only a reference and may require adjustment based on the developmental stage of the child and legal definitions of the age of majority between country jurisdictions. Recommendations include, but are not limited to, the core elements shown in Figure 16.

Figure 16: Six core elements to support transition care across specialities
(adapted from https://www.gottransition.org/six-core-elements)



Assessment of readiness may be formalised using readiness assessment questionnaires completed by both the child and caregivers to provide insight into their ability to cope with the transfer process and, therefore, represents a way of determining when the right time is for them to meet adult-focussed health-care providers [1546]. Adaptation of the six core elements to urology transition enables the creation of a checklist of active and resolved issues, operative reports and elements for conditions surveillance (i.e. surveillance imaging studies, blood work) and an updated inventory of renal function, continence status, fertility/sexual function, bowel function and psychosocial status [1546, 1551].

27.4 Specific genitourinary conditions

*27.4.1 **Neurogenic bladder***

Renal and bladder function are closely linked in children, and those presenting at an adult urological clinic may have evidence of dysfunction or deterioration (without or without reconstruction), which increases the risk of renal damage. There is a wide range of aetiologies for bladder dysfunction in childhood, including bladder outlet obstruction, smooth muscle/sphincter dysfunction, abnormal bladder function, and spinal cord/brain abnormalities. These dysfunctions may also be acquired and include recurrent UTIs, stones, trauma, chemotherapy and/or radiotherapy, and iatrogenic interventions. The most common cause for neurogenic bladders in adolescent and transitional clinics is spinal dysraphism, of which myelomeningocoele is the most likely to cause bladder and bowel dysfunction [1552]. With advances in neonatal and paediatric care, 50-94% of infants born with spina bifida are now estimated to survive into adulthood [1553]. This means that adult urologists are increasingly encountering such patients and are tasked with managing the urological manifestations of this condition and/or its treatments, with healthcare providers requiring more than a basic knowledge of neurogenic bladder management. Specific urological issues at transition require surveillance and management of renal function, urinary incontinence, urinary tract infections, bowel function, sexual function, urolithiasis, and complications from urinary tract reconstruction [1554]. The risk of bladder cancer following augmentation in children appears to be very low. However, the data from a systematic review analysing this data was only able to include two studies with more than five-years follow-up. Therefore, long-term oncological outcomes remain uncertain [1555].

Several studies have demonstrated ongoing, underlying issues at presentation to adult urological clinics in this cohort. A joint study from Utah and Minnesota in the United States demonstrated that 77% patients were performing intermittent catheterisation, with 84.6% having an identified urological problem, the most common of which was bothersome urinary incontinence affecting 52% patients. Overall, 97% required an intervention [1556]. Another study demonstrated that following attendance at a transitional care clinic for spina bifida, 71% of adolescent/adult patients required changes in bladder management and 38% underwent a major surgery [1557]. In Canada, only a minority of paediatric urologists perceive that the transition process should begin at the age of eighteen or older. However, there is no defined ongoing urological care as a component of this process, suggesting the potential for substandard quality of care [1558]. This is in contrast to the 2023 Spina Bifida Association's Transition to Adult Care Guidelines, which recommended that transition discussions should ideally begin at birth.

The process of transition is critical to a smooth transfer of care to adult services. A US study demonstrated that 40% patients had never wanted to transition, and that parents thought about this more than patients did. Only 34% patients had a transition plan, with the only significant predictor of transition being a history of urolithiasis [1559]. In a study examining sexual and reproductive health in adolescents with spina bifida, 95% patients stated that they had inadequate knowledge of these issues [1560]. Factors affecting transition readiness have included higher validated assessment scores (e.g. TRAQ; Transition Readiness Assessment Questionnaire), which is negatively associated with urinary incontinence, and positively associated with health literacy [1561, 1562]. Despite this, a study from the United States of transitioned adults with spina bifida demonstrated on TRAQ scoring showed that they were still not fully ready to transition, with males affected more than females. This suggested that an increased attention to transition readiness and consideration of a longer transition process in this population may be necessary [1563, 1564]. The frequency of clinic surveillance also appears important. Most adult spina bifida patients have symptomatic urological issues within a two-year follow-up interval, with 34% having significant issues within three years, which suggests a narrower interval frequency [1565]. The barriers to successful transition in spina bifida patients within TRAQ domains include 'appointment keeping' and 'tracking health issues,' as well as financial difficulties and the utilisation of community services. These indirect medical issues suggested that an increased awareness around transition readiness and the involvement of social work and specialist nursing were an integral part of the process [1566, 1567].

Several studies have shown improved outcomes in spina bifida patients who have undergone formal transition compared to an *ad hoc* referral to adult services, with much of this data currently originating from North America. A study from Texas reported improved adherence to bowel regimens at the time of transfer to adult care, along with better planning for decision-making and transportation to clinic appointments [1568]. A separate study from Michigan found that females were more likely than males to attend clinics following transition to adult services, while individuals who did not transition had comparable outpatient visit patterns but higher rates of inpatient and emergency care utilisation [1569]. A study from Indiana showed that spina bifida patients who transitioned tended to have more active health issues and more radiographic tests prior to discharge, and were less likely to use emergency department services, although there remained a significant issue with outpatient attendance compliance [1570]. However, a subsequent study from Oklahoma found that those who participated in a transition clinic were more successful in transferring from paediatric to adult care, with improved subsequent clinic attendances, and that early introduction to adult providers as well as an increased number of visits positively impacted compliance [1571]. It has been shown that transition readiness can be improved with clinic experience, and the relationship with the paediatric urologist can further facilitate this process [1572]. Overall, successful transition of spina bifida patients results in a relative decrease in unplanned hospital admissions, unplanned outpatient clinic attendances, and preventable emergency department visits [1573].

*27.4.2 **Posterior urethral valves***

Despite early intervention, many posterior urethral valves (PUV) patients have inherently abnormal bladders. The 'valve bladder' is a progressive condition that continues to evolve over years, despite surgically alleviated bladder outlet obstruction during infancy. Clinically, this can present as urinary incontinence or polyuria, due to poor bladder compliance, detrusor overactivity, VUR, ureterovesical junction obstruction or myogenic failure [1547, 1574]. It is essential to the adult urologist to recognise risk factors (dilatation of upper urinary tract, progressive loss of renal function, detrusor non-compliance) for progressive lower urinary tract dysfunction in adult men with PUV. Life-long monitoring, including serial renal function blood tests, upper tract imaging and urodynamic studies, has been advocated [1574]. Treatment options, analogous to neurogenic bladder patients, are tailored to the specific patient and includes behavioural modifications, nocturnal bladder emptying, pelvic floor muscle therapy, anticholinergics, CIC, alpha antagonist, and in selected cases, bladder augmentation [1574].

Chronic kidney disease develops in up to 32% of PUV patients and approximately 20% of these progress towards ESRD [1231]. Renal transplantation in these patients can be performed safely and effectively [1299, 1300]. Prior to transplantation, a full bladder and voiding assessment is recommended. Renal function should be monitored throughout life by both an adult urologist and a nephrologist [1547, 1574] (see Chapter 21 on congenital lower urinary tract obstruction).

*27.4.3 **Hypospadias***

Hypospadias is usually diagnosed and treated in early childhood. Being a dynamic condition, hypospadias and its surgical approaches to repair tend to pose continuing challenges with time. Appropriate long-term follow-up remains controversial, because most patients with hypospadias do well with minimal further urologic issues after initial repair [1548]. Penile development, especially during puberty, can result in new functional concerns. Additionally, some complications, including fertility, sexual dysfunction and cosmetic dissatisfaction, only become apparent as patients became sexually active [1547, 1575]. In adult hypospadias patients with urological issues, urethral strictures and lower urinary tract symptoms (45-72% and 50-82%, respectively) are the most commonly presenting conditions. This is followed by urethrocutaneous fistula (16-30%), uncorrected hypospadias (14-43%), spraying of the urinary stream (24%), UTI (15-25%), ventral curvature (14-24%), lichen sclerosus (8-43%), dysuria (10%), and general genital dissatisfaction [1575]. It is recommended that adult patients are, therefore, best addressed by a urethral reconstructive urologist, as a general urologist may have limited exposure to the complex urethral reconstructive procedures often required to address these issues [1547].

To lessen the difficulties in transitioning hypospadias patients from a paediatric to an adult urologist, follow-up throughout childhood and adolescence is advisable [1575]. Furthermore, it may be prudent to educate adolescent patients to enable them to take ownership of their condition and an awareness of prior surgical management (see Chapter 9 on hypospadias).

*27.4.4 **Bladder-exstrophy-epispadias complex***

The management of bladder exstrophy-epispadias complex (BEEC) in infants is well-established, and continence outcomes in specialist centres are well-described [1576]. On the contrary, adolescent and adult care is rarely formally centralised, even though similar complex challenges exist [1545]. Children with cloacal or bladder exstrophy may require bladder augmentation or diversion with closure of the bladder neck and the creation of a catheterisable channel. These children are at risk of long-term complications associated with the interposition of bowel segments into the bladder [1547, 1576]. In addition to urinary function, sexual and reproductive function can be impaired for both sexes. In men, dorsal penile curvature, a reduced corporal volume and a widened pubic symphysis can result in a short functional penile length. Men with epispadias can also experience difficulties with retrograde ejaculation. In women, vaginal stenosis (31%) and pelvic organ prolapse may be present. Pregnancy is possible but with an increased risk of preterm labour. Scheduling these patients for an elective caesarean section should be considered to avoid potential complications associated with spontaneous vaginal delivery [1545, 1547, 1548, 1577].

Individuals with BEEC are at an increased risk of developing cancer, with the majority being diagnosed at a younger age compared to the general population and typically presenting with nonurothelial types [1576, 1578, 1579]. A systematic review indicated that 56% of BEEC patients with cancer are diagnosed between the ages of 45 and 67, while 37% are diagnosed between 0 and 44 years of age. The male-to-female ratio among these patients is 2.7:1, and adenocarcinoma accounts for 68% of the tumour types identified [1578]. Although screening for symptoms of urothelial cancers in individuals with BEEC has been suggested, no standardised surveillance protocols have been established to date [1576, 1578].

Due to the complexity involved in the management of the paediatric BEEC patient, a similar transitional approach and infrastructure is recommended for this cohort who transition to adult care [1577].

*27.4.5 **Differences of sex development***

Differences of sex development (DSD) encompass a broad spectrum of diagnoses, of which the majority of individuals present with ambiguous genitalia at or shortly after birth and are cared for by paediatric services throughout childhood. However, a proportion of children with DSD present in early adolescence and spend only a short time in paediatric care before transition to adult services.

During transition, a general move towards independence and self-responsibility is pertinent, as is a more specific focus on discussing the DSD diagnosis with the individuals themselves, along with the details of any treatment history and potential further management as the individuals mature [1580, 1581]. Studies of children with congenital adrenal hyperplasia (CAH) have shown that providing the adolescent with knowledge regarding

the pathophysiology of CAH, an understanding of their medication regimen, skills to self-manage stress-dose steroids during illness, knowledge of sexual function, and fertility expectations has empowered these children to take primary responsibility for their care and transition into adulthood [1582]. It has also been shown that transition readiness is higher among CAH adolescents with good medication-adherence rates [1583]. Transitional care for children with DSD requires continuity of an expert multidisciplinary team, supporting the child and their families in an environment comprising specialists (endocrinology, surgery, urology, psychology/psychiatry, gynaecology, genetics, social work and nursing) with experience from both paediatric and adult practice (See Chapter 20 on disorders/difference of sex development).

27.5 Summary of evidence and recommendations for transitional urology

Summary of evidence	LE
There are several paediatric urological conditions requiring long-term follow-up that would be unfamiliar to solely adult-trained urologists.	4
Involvement of paediatric and adult urologists working in a multidisciplinary team with expertise in the management and treatment of congenital conditions is essential.	4
Assessment of readiness may be formalised using readiness assessment questionnaires completed by both the child and caregivers to provide insight into their ability to cope with the transfer process and, therefore, represents a way of determining when the right time is for them to transition to adult services.	4
A gradual introduction of the adult urologist into the health care team, several years before targeted time of transition, may facilitate the transition.	4

Recommendations	Strength rating
Develop a standardised transition-of-care program and collaborate with adult providers to facilitate safe, successful and sustainable transition.	Strong
Start transition at the onset of adolescence involving both paediatric and adult urology providers in a multidisciplinary approach to ensure better transition readiness and subsequent adult clinic adherence.	Weak
Use a validated transition assessment tool to objectively assess for transition readiness.	Strong

28. FOETAL UROLOGY

28.1 Normal renal development

*28.1.1 **Introduction***

Congenital urogenital anomalies account for approximately 20-30% of all abnormalities detected on prenatal ultrasonography, with urinary tract malformations being the most frequent within this group [1584-1588]. These anomalies range from mild findings, such as low-grade hydronephrosis, to conditions incompatible with life, such as bilateral renal agenesis. Over recent decades, prenatal diagnosis has advanced considerably due to the widespread use of second- and third-trimester ultrasonography and, increasingly, foetal magnetic resonance imaging as a complementary tool. Early detection enables delivery planning in tertiary centres with multidisciplinary teams. It also allows tailored postnatal management aimed at reducing neonatal morbidity and optimising long-term renal prognosis. Accurate interpretation of congenital anomalies requires knowledge of normal urinary tract embryology and the principal aspects of imaging assessment. Prenatal findings provide essential information for parental counselling and perinatal planning. Families should be informed not only about the immediate anatomical findings but also about the possible impact on renal and/or bladder function, associations with genetic or syndromic conditions, and implications for neonatal management [1589, 1590]. This highlights the role of prenatal imaging as both a diagnostic and a prognostic tool, while underscoring its limitations. At the same time, it is important to communicate that prenatal diagnoses are not necessarily definitive and may require postnatal confirmation to establish the exact nature and severity of the condition.

*28.1.2 **Renal and bladder development***

28.1.2.a Normal development

The kidneys develop from the intermediate mesoderm through three successive stages, with the metanephros forming the permanent kidney. Migration from the pelvis to the lumbar region occurs between weeks 6 and 9, and abnormal interaction or ascent may result in ectopia, fusion anomalies such as horseshoe kidney, or renal agenesis [1589, 1591, 1592]. Complete failure of ureteric bud induction may result in unilateral or bilateral renal agenesis [1591]. Persistence of embryonic vessels may lead to accessory renal arteries, which in some cases can contribute to ureteropelvic junction obstruction [1592].

Corticomedullary differentiation becomes progressively more visible with advancing gestation and should be routinely assessed during prenatal imaging [1589].

The urinary bladder originates from the anterior cloaca and can usually be identified from 9 to 10 weeks as a midline anechoic structure that fills and empties regularly. The visualisation of the urinary bladder confirms the presence of at least one functioning kidney and offers an early indirect marker of urinary tract patency [1589].

Understanding normal renal and bladder development is essential for interpreting their appearance on prenatal imaging.

28.1.2.b Prenatal ultrasound

Prenatal ultrasound is an essential technique for monitoring foetal development and detecting congenital anomalies. Although the frequency and timing of these examinations vary between countries, there is broad consensus that all pregnant women should undergo at least one ultrasound in the first trimester and another in the second trimester, while the use of a third-trimester scan depends on national recommendations.

While ultrasound remains the cornerstone for detection of urinary tract malformations, its accuracy can be limited by maternal factors, oligohydramnios or when complex malformations are suspected. In such situations, foetal MRI can provide complementary information to better define anatomy and guide counselling [1593].

- **First trimester (11-14 weeks)**

During this period, the main objectives of ultrasound are to confirm pregnancy viability, establish accurate gestational age and initiate screening for aneuploidy and early preeclampsia [1594-1596]. In addition, first-trimester ultrasound can identify some major structural anomalies. Early recognition of such findings enables earlier genetic testing and provides more time for parental counselling and decision-making. When an anomaly is detected or suspected at this stage, the patient should be referred to a specialised centre without waiting for the midtrimester scan [1589, 1590].

The urinary bladder should always be visible from 12 weeks onwards with a longitudinal diameter < 7mm [1228, 1594]. Persistent no visualisation at this stage may suggest bilateral renal agenesis, cloacal exstrophy or bladder exstrophy, and requires repeat scanning for confirmation. The kidneys are usually detectable from 12 to 13 weeks in a paravertebral position, with reniform morphology and a central hypoechoic pelvis. The echogenicity of kidneys is compared to that of the liver and spleen. Ureters are not normally visible [1589].

The most characteristic urinary malformation detectable in this period is megacystis, which is defined as a bladder diameter ≥ 7mm between 11 and 14 weeks. If the bladder diameter measures between 7 and 15mm, this is considered mild megacystis. Such cases carry an increased risk of aneuploidy, but a spontaneous resolution is likely. For this reason, a follow-up ultrasound within one week is recommended to confirm progression or resolution [1590, 1596]. If the diameter exceeds 15mm, the probability of significant lower urinary tract obstruction (CLUTO) is considered high. In these cases, the bladder is markedly enlarged and the 'keyhole sign' (distension of the proximal urethra) may be seen, with secondary effects on the kidneys (enlargement and increased echogenicity) and dilatation of the ureters [1589, 1590].

Although amniotic fluid depends primarily on maternal origin in the first trimester and does not yet reflect foetal renal function, severe forms of LUTO can later evolve into oligohydramnios and pulmonary hypoplasia, which carry major prognostic implications [1589].

- **Second trimester (18-22 weeks)**

The second trimester represents the period of highest diagnostic yield for structural anomalies. The mid-trimester scan, performed between 18 and 22 weeks, is the key morphological assessment and allows detection of most clinically relevant urinary tract anomalies [869, 1585, 1590]. At this stage, amniotic fluid volume mainly reflects foetal renal function, serving as an indirect functional marker.

Normal sonographic findings

Both kidneys should be bilaterally visible in the paravertebral region, with reniform morphology and clear corticomedullary differentiation. Echogenicity should be equal to or lower than that of the liver; diffuse hyperechogenicity suggests dysplasia. The renal pelvis is physiologically <4mm in the second trimester, whereas an anteroposterior diameter of ≥7mm is pathological [869, 1590]. Kidney length correlates with gestational age, although longitudinal growth in growth-restricted foetuses may remain normal while transverse and anteroposterior dimensions are reduced [1585].

The urinary bladder should always be present, showing filling and emptying cycles. Longitudinal measurements average ±14mm at 18 weeks and ±23mm at 22 weeks [1597]. The urinary bladder should not extend above the umbilical cord insertion. Persistent nonvisualisation requires exclusion of severe anomalies such as bladder or cloacal exstrophy. The umbilical cord insertion site and the presence of two umbilical arteries should be documented - a single umbilical artery, although nonspecific, has been associated with complex anomalies [1228].

Key urological anomalies:

- Urinary tract dilatation: most frequent abnormality. Anteroposterior diameter (APD) ≥7mm is pathological and requires follow-up.
- Persistent megacystis: persistence beyond the first trimester almost always indicates CLUTO. The bladder is markedly distended and fails to empty, often with a 'keyhole sign.' Secondary findings include enlarged hyperechoic kidneys, ureteral dilatation and ultimately oligohydramnios [1589, 1590, 1596].
- Renal agenesis: unilateral cases present with normal bladder with filling and emptying cycles and amniotic fluid. Bilateral agenesis leads to absent bladder and kidneys, progressive anhydramnios after 20 weeks, and a universally poor prognosis.
- Multicystic dysplastic kidney (MCDK): multiple noncommunicating cysts replace normal parenchyma. Bilateral cases or those associated with contralateral agenesis have poor outcome, while unilateral cases with a normal opposite kidney usually evolve favourably.
- Diffuse renal dysplasia: diffuse hyperechogenicity with loss of corticomedullary differentiation.
- Polycystic kidney disease:
    - ARPKD: massively enlarged, hyperechoic kidneys and early renal failure.
    - ADPKD: enlarged, hyperechoic kidneys, usually with normal amniotic fluid, and postnatal manifestation.
- Duplex collecting system and ureterocoele: duplication anomalies may occasionally be seen. A ureterocoele appears as a cystic lesion within the bladder and is highly suggestive.
- Isolated renal cysts: simple anechoic cysts within otherwise normal kidneys, generally with favourable prognosis.
- Visible ureteral dilatation: always pathological, indicating obstruction or reflux.

- **Third trimester (30-32 weeks)**

The third-trimester ultrasound aims to monitor previously identified findings and detect anomalies that may only become apparent at this stage [1585].

Normal findings

Kidneys are normally reniform in shape and located in the paravertebral region.

Corticomedullary differentiation becomes clearer and more consistent than in the second trimester, reflecting progressive parenchymal maturation. On ultrasound, the cortex has intermediate echogenicity compared to the liver, the medulla is more hypoechoic, and the renal pelvis appears as a central hypoechoic zone.

An anteroposterior renal pelvic diameter (APRPD) of <7mm is considered normal, while ≥7mm is abnormal. An APRPD of <15mm carries a low risk for the need for postnatal intervention, and the risk for a urological condition increases with severity of the dilatation above this cut-off [867, 1598, 1599].

The urinary bladder should always be visible, showing filling and emptying cycles, without wall thickening.

Amniotic fluid volume becomes a key indirect marker of foetal renal function.

Key urological findings in late gestation:

Third-trimester hydronephrosis: approximately 60% of cases are first detected during this period. Prognosis is poorer when oligohydramnios is present [1590].

- Renal cysts and dysplasia: better defined at this stage, presenting as diffuse hyperechogenicity, thinned parenchyma, and multiple noncommunicating cysts replacing the normal renal structure [1585, 1590].
- Lower urinary tract obstruction: can be reassessed to determine progression. Lower urinary tract obstruction presents with a massively distended bladder with thickened wall, bilateral ureteral dilatation, blow-out of the urinary tract, and in some cases, oligohydramnios [1596, 1600].
- Autosomal dominant polycystic kidney disease (ADPKD): the third trimester is the most common period of prenatal presentation. Kidneys are enlarged, with variable echogenicity and altered corticomedullary differentiation. Cysts may or may not be visualised [1585, 1590].

28.1.2.c Foetal magnetic resonance imaging

- **Indications:**
  Foetal MRI is indicated when ultrasound findings are inconclusive or when there is suspicion of a complex anomaly that cannot be fully characterised sonographically. Foetal MRI is therefore considered a complementary technique rather than a screening tool [1593, 1601].
- **Timing:**
  The diagnostic performance of MRI is limited before 18-20 weeks of gestation. The optimal window is between 26 and 32 weeks, when renal parenchyma, cysts and dilatations are more easily assessed and pulmonary development can also be evaluated [1593].
- **Normal appearance:**
  On T2-weighted sequences, normal kidneys appear as reniform structures of intermediate signal intensity with a central hypointense zone corresponding to the renal pelvis. Corticomedullary differentiation becomes progressively evident as gestation advances. Renal cysts are visualised as well-defined hyperintense lesions. The urinary bladder is identified as a midline hyperintense spherical or ovoid structure with changes in size according to filling and emptying cycles. Normal ureters are generally not visible; their detection usually indicates pathological dilatation [1601, 1602].
- **Safety:**
  Foetal MRI is considered safe during pregnancy when performed at the magnetic field strengths routinely used in clinical practice, with no evidence of adverse foetal effects in large observational series [1603]. The administration of gadolinium-based contrast agents is contraindicated, as gadolinium crosses the placenta and may accumulate in amniotic fluid and foetal tissues, raising concerns about potential teratogenic and toxic effects. In addition, maternal anxiety or emotional distress during the examination has been reported, underscoring the importance of adequate pre-test counselling and support [1604].
- **Diagnostic contribution:**
  Several studies have demonstrated that MRI can provide decisive information that directly impacts prenatal counselling and management:
  - **Differentiation of multicystic dysplastic kidney (MCDK) from severe hydronephrosis** [1593].
  - **Characterisation of abdominal wall and pelvic anomalies,** including the bladder exstrophy-epispadias complex, when ultrasound is inconclusive [1605-1607].
  - **Evaluation of pulmonary volume and morphology** in severe lower urinary tract obstruction (CLUTO) or prune belly syndrome, where prognosis depends on both renal and pulmonary status [1608, 1609].
  - **Distinction between unilateral MCDK and bilateral cystic kidney disease,** an important determinant of postnatal prognosis [1602, 1610].

28.1.2.d Genetic counselling and multidisciplinary approach

This section addresses the key questions related to genetic counselling in foetal urological anomalies: when genetic counselling should be recommended, which types of genetic workup are appropriate, and which conditions indicate its use.

28.1.2.d.1 Genetic testing in the prenatal diagnosis of CAKUT

In genetic counselling, it is important to distinguish between screening and diagnostic tests. Non-invasive screening with cell-free foetal DNA (cfDNA) in maternal blood allows the detection of common aneuploidies but does not identify structural urological anomalies. When a significant ultrasound finding is present, genetic diagnosis is only possible through an invasive test that analyses foetal material directly (amniocentesis at/or beyond 15 weeks GA or chorionic villus sampling after ten weeks GA), which enables chromosomal microarray (CMA) and, when indicated, more advanced sequencing studies (WES).

Genetic evaluation forms an integral part of the management of congenital anomalies of the kidney and urinary tract (CAKUT) detected prenatally. Molecular testing refines prognostic accuracy, facilitates the identification of syndromic entities with extrarenal involvement, and provides essential information for reproductive counselling, including recurrence risk and consideration of preimplantation or prenatal testing in future pregnancies [1611].

28.1.2.d.2 ***Family counselling***

A prenatal diagnosis of a urological anomaly imposes a considerable emotional burden on families, who frequently report anxiety and a strong need for clear, realistic prognostic information. Counselling should be structured, reiterated across several consultations, and tailored to family circumstances. Counselling must also address reproductive implications and ensure access to psychological support and written educational resources [1611-1613]. Importantly, families should be informed that prenatal findings may not always be definitive and that the working diagnosis will be verified and refined after birth. Finally, genetic counselling and multidisciplinary decision-making should always be adapted to the cultural, ethical and legal context of each country, ensuring that parental values and local regulations are fully respected in the counselling process.

28.1.2.d.3 ***The multidisciplinary team (MDT)***

Optimal management requires a multidisciplinary team (MDT), including maternal-foetal medicine specialists, clinical geneticists, paediatric urologists and nephrologists, neonatologists and psychologists. This integrated approach ensures comprehensive evaluation and consensus-based planning. Severe LUTO represents a classical example where prognosis is uncertain and the potential for foetal intervention illustrates the complexity of decision-making, underlining the essential role of MDT discussion and referral to specialised centres [1611, 1614].

28.2 Antenatal hydronephrosis

28.2.1 ***Definitions and follow-up during pregnancy***

Antenatal hydronephrosis (ANH) is defined as a prenatally detected dilatation of the renal pelvis and is a common finding in 1-2% of pregnancies [1590, 1615]. Antenatal hydronephrosis is more often seen in male foetuses compared to female foetuses at a rate of approximately 3:1 [1599, 1616-1618]. The anterior-posterior renal pelvic diameter is commonly used to quantify ANH on foetal ultrasound. An APRPD that exceeds 4mm and 7mm before and after 28 weeks, respectively, is considered dilated [1619]. The ureters are considered dilated when visible [1615].

There is a large variety of clinical presentations of ANH, with a majority being transient findings (up to 80%) and others indicating more severe postnatal outcomes where surgical intervention is needed [1590]. Prenatal parameters such as parenchymal appearance, kidney size and echogenicity, and amniotic fluid volume, as well as selected foetal urinary biochemical markers (e.g. sodium, chloride, β2-microglobulin, cystatin C), may provide supportive information regarding postnatal renal function, but their predictive value remains variable [1620].

ANH has also been associated with chromosomal anomalies, single-gene disorders, and other congenital malformations, including digestive anomalies [1621]. When relevant, genetic counselling and testing should be offered based on ultrasound findings and family preferences [1622].

28.2.2 ***Aetiology***

Antenatal hydronephrosis can present in isolation but may also be associated with abnormalities of the ureters, bladder or renal parenchyma, and is considered part of the congenital anomalies of the kidneys and urinary tract (CAKUT). Possible diagnoses that are found after birth in children with ANH include ureteropelvic junction obstruction (UPJO), duplex kidney, poly- or multicystic kidney (P/MCDK), vesicoureteral reflux (VUR), posterior urethral valves (PUV), ectopic ureter, ureterocoele and ureterovesical junction obstruction (UVJO) [1618, 1623, 1624]. UPJO represents the most common underlying diagnosis in cases with isolated ANH, whereas the presence of additional anomalies typically prompts more extensive postnatal investigations to clarify the underlying pathology [1625]. Figure 17 presents a proposed management pathway to differentiate between the possible diagnosis during the pre- and postnatal period [1625].

28.2.3 ***Classification systems for postnatal outcomes***

Two classification systems are most often used to determine the severity of ANH and to support risk stratification for postnatal outcomes. The SFU grading system includes the Renal Pelvis Anteroposterior Diameter (RPAPD), collecting systems and renal parenchymal appearance [1626]. The urinary tract diameter (UDT) classification system can be used both ante- and postnatally and additionally assesses other parameters in the urinary tract, e.g. aspect of ureters and bladder compared to the SFU system [1590]. Tables 14 and 15 summarise both classification systems. A comparison between these classification systems demonstrated that both systems allow a proper risk stratification and prediction of clinical outcomes [1627].

The Hydronephrosis Severity Index (HSI), an artificial intelligence-based tool, has shown promise in predicting the presence of obstruction based on ultrasound images and SFU grading. While this may assist in decision-making regarding follow-up, its clinical use remains investigational [1628].

*28.2.4 **Postnatal outcomes***

When ANH is diagnosed, counselling should emphasise the range of possible postnatal outcomes and the fact that prenatal findings may not be definitive. Differentiating between isolated ANH, bilateral ANH and ANH associated with other CAKUT is important for planning follow-up. Various predictive factors have been described and are now summarised. A spontaneous resolving ANH during pregnancy resulted in a recurrent postnatal hydronephrosis in 44% of children. However, none of these patients required surgical intervention during follow-up [1629].

- The **Anteroposterior Renal Pelvic Diameter (APRPD)** is commonly used as a marker to assess postnatal risk. In children with an isolated APRPD of <20mm, spontaneous resolution rates of 72% have been described, with higher resolution rates for lower APRPD [1630]. Larger APRPD values and increasing measurements during gestation have been associated with a higher likelihood of postnatal intervention [1599, 1618]. A cut-off of 15mm has been proposed in some studies, but no single threshold is absolute, and decisions must be guided by the overall clinical and imaging context. The presence of associated CAKUT further increases the likelihood of intervention or abnormal outcomes compared to isolated ANH [1599].
- The **Urinary Tract Dilation (UTD) classification system** can be used to predict postnatal outcome, and outcomes vary whether ANH is isolated or in concurrence with additional abnormalities. Resolution rates for UTD A1 of 73% and resolution rates of 21% for A2/A3 have been demonstrated [1631]. The need for additional treatment antibiotics/surgery becomes higher with increasing UDT grade [1631]. In isolated ANH, the need for surgery was shown to be lower when using the UDT classification P1 1% and P2/P3 31% [1627]. The rate of UTI was lower in the P1 group with 2% compared to 10% in P2/P3 [1627].
- The **SFU classification system** has been used to predict resolution and need for surgery. Grouping often occurs with grade 1-2 classified as low and grade 3-4 as high. Lower SFU grades have higher chances to resolve spontaneously and less often require surgery [1623, 1632]. Spontaneous resolution rates are per grade: SFU grade 1 89-94%; grade 2 57-77%, grade 3 34.4-46% and grade 4 11% [1616, 1630]. Need for surgery has been reported to be 2-15% for low grades and 32-77% for high grades, with lower ages at surgery for higher SFU grades [1616, 1617, 1627].

*28.2.5 **Long-term outcomes***

Long-term follow-up studies suggest that outcomes correlate with UTD grade, but variability exists. In one nine-year follow-up study of isolated ANH, surgical intervention and UTI rates increased with UTD grade, whereas no hypertension, CKD or renal injury was observed in children with UTD P1 [810]. Children with higher grades (P2 and P3) showed higher frequencies of hypertension, CKD and renal injury, but these associations should be interpreted in the context of study heterogeneity and selection bias. A separate 13-year follow-up reported variable surgical needs and UTI rates depending on the underlying anomaly [1624].

*28.2.6 **Prophylactic measures against UTIs***

Two systematic reviews found no proven benefits for continuous antibiotic prophylaxis in the heterogeneous group of children with ANH involving all various aetiologies. However, individual risk stratification is warranted with children with risk factors such as ureteral dilatation, circumcision status, girls and high-grade ANH [825, 1633]. Circumcision was found to reduce the frequency of UTIs in boys with isolated ANH, ANH secondary to VUR and ANH secondary to PUV in a different systematic review [1634]. Additional measures, such as foreskin care and topical steroid use, may further reduce UTI risk in selected cases [1635].

Table 14: Society for Foetal Urology (SFU) classification system

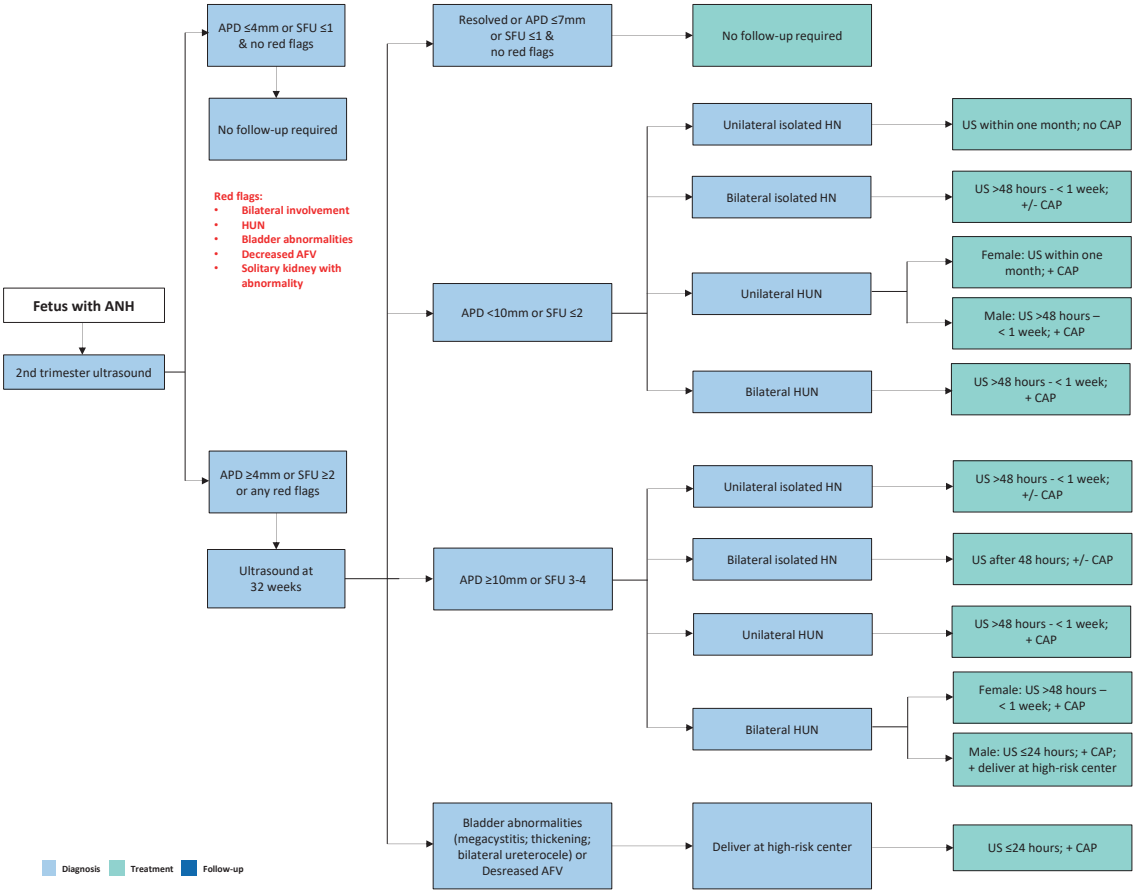
SFU grading system	
0	No hydronephrosis
1	Dilatation of renal pelvis only, with no calyceal involvement or parenchymal atrophy
2	Dilatation of both the renal pelvis and some calyces.
3	Significant dilatation of the renal pelvis and all calyces, along with a mild thinning of the renal cortex
4	Gross, balloon-like dilatation of the renal pelvis and calyces, with marked loss of the border between them and visible thinning of the renal parenchyma

Table 15: The Urinary Tract Dilation (UTD) classification system (adopted from Nguyen *et al.*, 2022 [1590]

	Antenatal		**Postnatal (> 48h)**		
	UTD A1	**UTD A2-3**	**UTD P1**	**UTD P2**	**UTD P3**
APRPD	4-<7mm (<28w) 7-<10mm (≥28w)	≥7mm (<28w) ≥10mm (≥28w)	10-<15mm	≥15mm	≥10mm
Calyces		Any dilatation	Central dilatation	Peripheral dilatation	Any dilatation
Ureter		Any dilatation (with APRPD≥4mm or calyceal dilatation)		≥4mm (with APRPD≥10 mm or calyceal dilatation)	
Parenchymal abnl., Bladder abnl., or Oligohydramnios		Yes (with APRPD ≥4mm or calyceal dilatation)			Yes

APRPD = Anterior Posterior Renal Pelvic Diameter.
Parenchymal abnormalities = cortical thinning, hyperechogenicity, or cystic dysplasia, indistinct corticomedullary differentiation.
Bladder abnormalities = wall thickening, ureterocoele, dilatated posterior urethra.

Figure 17: Diagnostic and management pathway for foetuses with ANH
(Adapted from Rickard *et al.*, 2022) [1625]



AFV = amniotic fluid volume; APRPD = anteroposterior renal pelvic diameter; CAP = Continuous antibiotic prophylaxis; HN = Hydronephrosis; HUN = Hydroureteronephrosis; SFU = Society for Fetal Urology grading system; US = Ultrasound.

28.3 Congenital lower urinary tract obstruction

*28.3.1 **Introduction***

The term congenital lower urinary tract obstruction is used to refer to intrauterine dilatation of the bladder and/or the upper urinary tract. This condition affects roughly 2-3/10,000 births [1233, 1636]. The three most common causes include posterior urethral valves in males, urethral atresia or urethral stenosis [1637]. The outflow obstruction of the bladder in children with CLUTO leads to progressive bladder dilatation, bladder wall thickening, hydroureteronephrosis with subsequent compression of the renal parenchyma and/or oligo- or anhydramnios [1228]. Oligo- and especially anhydramnios can compromise pulmonary development and result in pulmonary hypoplasia, especially in or before the critical period of lung development (canalicular phase, 16-24 weeks) [1638]. The presence of CLUTO in a foetus is therefore associated with a high morbidity and pre- and perinatal mortality [1233].

Due to the heterogeneity and the rare spectrum of clinical manifestations of CLUTO, referral of such cases is recommended to a tertiary centre with multidisciplinary expertise in prenatal and postnatal management of obstructive uropathies [1228].

This section deals with the prenatal diagnosis and prenatal management of foetuses with CLUTO. Details on postnatal diagnostics, management and outcomes can be found in Chapter 21 on congenital lower urinary tract obstruction.

28.3.2 ***Diagnosis***

28.3.2.a Ultrasound parameters

CLUTO is usually suspected or diagnosed during the routine prenatal ultrasound check-ups. Ultrasound is the first-line diagnostic tool in foetuses with suspected CLUTO. However, in some circumstances, when technical ultrasound conditions are poor, foetal MRI may provide additional information [1247].

The following ultrasound features can help discern an obstructive pathology from isolated hydronephrosis: Megacystis, defined as a longitudinal bladder diameter of ≥ 7mm in the first trimester and ≥ 15mm in the second trimester [1228]. Bladder wall thickening, dilated posterior urethra (keyhole sign), bilateral hydroureteronephrosis [1639] and oligo- or anhydramnios [1228, 1597]. However, differentiation between obstructive and nonobstructive aetiologies on prenatal US is challenging, as both have a similar sonographic appearance [1245].

Oligohydramnios is defined (beyond 16 weeks GA) as the deepest vertical pocket of amniotic fluid ≤ 2cm, anhydramnios as complete absence of amniotic fluid [1597]. Anhydramnios before 20 weeks gestation is a strong predictor of pulmonary hypoplasia and of foetal and neonatal death with survival rates of just 15-24% in this group [1228]. Therefore, the GA at the appearance of oligo- or anhydramnios is an important predictive factor [1597].

28.3.2.b Biomarkers

As an addition to ultrasound parameters, foetal urinary biomarkers can be measured. This measurement is usually performed as a serial vesicocentesis. The idea behind this being that the first puncture most likely represents old urine, whereas the sampling done 24 and 48 hours later represents newer urine and offers an idea of bladder cycling. Common elements evaluated in foetal urine chemistries include sodium, chloride, calcium, protein, osmolality and beta-2 macroglobulin, with normal reference values shown in Table 16.

Additionally, foetal serum beta-2 microglobulin appears to have a high sensitivity (80-100%) and specificity (66-99%) in predicting postnatal renal function [1640], particularly in late gestation. As it does not cross the placenta, foetal serum beta-2 microglobulin represents foetal renal function without the influence of maternal renal function and is not dependent on gestational age [1641]. Studies have shown that beta-2-microglobulin levels above 5mg/L appear to be a predictor of postnatal renal impairment [1640-1642]. However, it cannot be used to determine the benefit of foetal intervention with regards to improvement of renal function [1637].

More recently, a 12-peptide signature (12 PUV) has been designed by proteome analysis of foetal urine. It specifically identifies foetuses who would develop ESRD before the age of two years. The final validation of the 12 PUV signature is currently ongoing [1643]. Foetal urinary peptides to predict postnatal outcome of renal disease in foetuses with posterior urethral valves (PUV) [1643, 1644].

Table 16.: Favourable foetal urine chemistry (reproduced from Menchaca *et al.*, 2024) [1637]

Foetal urinary marker	Value
Sodium, mEq/L	< 100
Chloride, mEq/L	< 90
Calcium, mg/dL	< 8
Protein, mg/dL	< 20
Osmolality, mOsm/L	< 200
Beta-2 microglobulin, mg/dL	< 6

28.3.3 ***Management***

28.3.3.a Indication for Treatment and Staging systems

Goals of foetal intervention in CLUTO include improvement of foetal and neonatal survival, as well as improvement of postnatal kidney and bladder function. Before considering foetal intervention, life-limiting genetic or structural anomalies should be excluded [1597].

Indications for foetal intervention in CLUTO include ultrasound findings suggestive of obstruction and reduced amniotic fluid volume. Additional factors such as bladder refill and renal biochemistry can be taken into consideration for decision-making [1597].

Multiple staging systems for the estimation of the severity of the prenatal obstruction and guidance on indicating prenatal intervention have been proposed. However, there is currently no recommendation to adopt any one of these staging systems into clinical practice yet [1597].

The staging system proposed by Ruano *et al.* includes ultrasound parameters and foetal urinary biomarkers. The proposed system includes four stages of LUTO severity. Stage II and III foetuses are potential candidates for foetal intervention. Stage IV represents foetal renal failure leading to anhydramnios and pulmonary hypoplasia. No foetal intervention is recommended, and further studies are needed to determine the role of amnioinfusion in this population [1252].

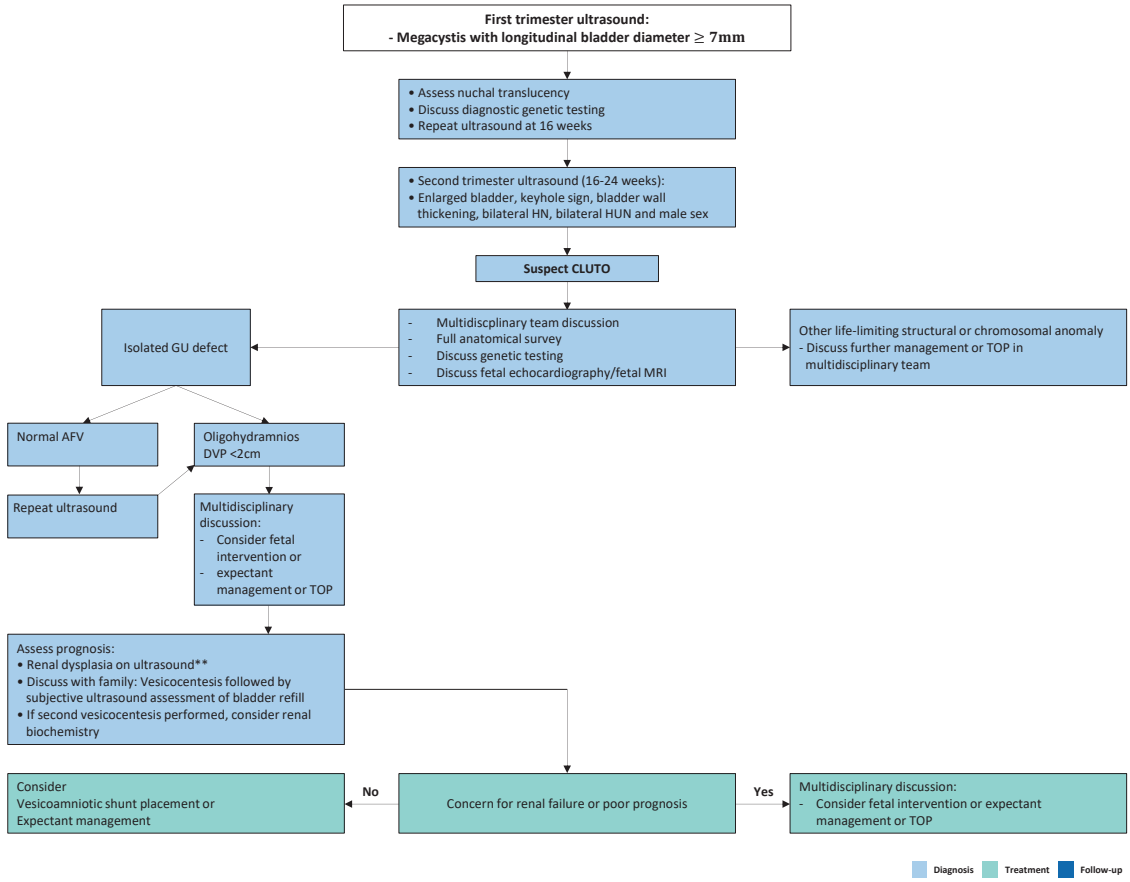
The staging system proposed by Fontanella *et al.* is based solely on ultrasound parameters and uses amniotic fluid volume (AFV) and bladder volume (BV) to determine severity of foetal LUTO. LUTO cases with a BV ≥ 5.4cm^3 or abnormal AF before 20 weeks' gestation were defined as severe and those with BV < 5.4cm^3 and still normal AF at the 20 weeks' scan were defined as moderate. Risk of perinatal mortality significantly increased according to the stage of severity [1645].

Table 17: Staging systems for the estimation of the severity of CLUTO

Ruano *et al.* **2017**	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Ultrasound	Normal AFI. No renal cysts or dysplasia	Oligohydramnios, severe bilateral hydronephrosis. Absent cysts or dysplasia	An- or oligohydramnios. Hyperechogenic kidneys, renal cysts; and/or dysplasia	Anhydramnios and anuria after monitoring bladder refilling rate. Renal dysplasia and hyperechogenicity
Biochemistry	Favourable after sequential sampling	Favourable after maximum of 3 sequential samplings	Unfavourable after sequential sampling	Unfavourable biochemistries and documented anuria
Possible foetal therapies	Weekly US monitoring	Cystoscopy or VAS	VAS with possible Amnioinfusion	Amnioinfusion
Fontanella *et al.* **2021**	**Stage I**	**Stage II**	**Stage III**	
Ultrasound	Normal AFV at 26 weeks	Bladder volume < 5.4cm^3 and/or normal AFV at 20 weeks	Bladder volume ≥ 5.4cm^3 and/or oligohydramnios or anhydramnios before 20 weeks	

AFI = Amniotic fluid index; AFV = amniotic fluid volume; US = Ultrasound; VAS = Vesicoamniotic shunting..

Figure 18: Management pathway for foetuses with suspected CLUTO (as suggested by Mustafa *et al.*) [1597]



AFV = amniotic fluid volume; CLUTO = Congenital lower urinary tract obstruction; DVP = Deepest vertical pocket; GU = Genitourinary; HUN = Hydroureteronephrosis; MRI = Magnetic resonance imaging; TOP = Termination of pregnancy.

- **Timing of intervention**

Foetal intervention can be performed in selected cases with moderate and severe CLUTO, ideally before 27 weeks of gestation [1228]. Historically, the ideal timeframe was said to be 16-27 weeks, which represents a vulnerable phase during lung development (canalicular phase).

However, newer studies suggest that early intervention in the first trimester (<14 weeks) is feasible, though technically more challenging and might better preserve renal function. The indication for performing an early intervention in published case series is foetal megacystis ≥15mm in the first trimester. Late intervention performed >17 weeks is thought to improve survival and postnatal pulmonary function but cannot prevent kidney damage [1646].

- **Techniques**

The most common techniques for foetal intervention in CLUTO include vesicoamniotic shunting (VAS), foetal cystoscopy and serial amniotic infusions.

- **Vesicoamniotic shunting**

The most common intervention in foetuses with CLUTO is vesicoamniotic shunting (VAS). In VAS, the foetal bladder is punctured under ultrasound guidance. A drainage catheter is then introduced with one end in the bladder and the other end in the amniotic cavity [1228]. Various stenting systems are available, subject to clinician preference. The rationale of VAS is to bypass the obstruction and ensure amniotic fluid cycling by continuous drainage of the bladder into the amniotic cavity. This prevents oligo- and ahydramnios and subsequent pulmonary hypoplasia [1647].

An SR and meta-analysis on the outcomes of 'late' foetal interventions (16-28 weeks) including 10 studies showed an improved perinatal survival of the VAS group compared to the control group (57% vs. 38.8%) [1256, 1263]. Subgroup analysis showed that perinatal survival was improved in foetuses with unfavourable urine chemistry, however, not in those with favourable urine chemistry.

The studies reporting on postnatal renal function showed a trend for a higher postnatal renal function in the VAS group compared to the conservative group at six months to two years postnatally [1256].

Newer studies suggest that early intervention before 16 weeks might achieve a higher rate of normal renal function and pulmonary function peri- and postnatally compared to later treatment [1257]. Supporting this notion are case series that show a higher overall survival rate, reported as 74% [1646], and a higher rate of foetuses with preserved perinatal renal function in 51% [1648]. However, a higher proportion of complex urethral pathologies was found in the early shunting group, posing new clinical challenges in the postnatal period [1649].

Procedure-related complications of VAS are very high with reported rates of up to 40%. Most common complications include shunt dislocation or retraction, shunt blockage, foetal ascites and premature rupture of membranes [1263]. Surgical removal of shunts was necessary in more than half of newborns after early shunt placement due to shunt migration [1650, 1651].

*28.3.4 **Foetal cystoscopy***

Foetal cystoscopy with laser ablation of the PUV has been reported as an alternative treatment to VAS. Two SR on this topic show improved survival in the treatment group comparing to the group without treatment [1256, 1652]. However, numbers are small and urological fistulas have been reported in up to 10% of patients. The evidence on foetal cystoscopy is limited to case series with a limited number of patients. Therefore, no clear recommendations can be made.

*28.3.5 **Serial amniotic infusions***

Serial amnioinfusions were first described in the 1990s in the setting of preterm premature rupture of the membranes (PPROM) [1653]. However, the role of serial amnioinfusions in foetuses with LUTO remains experimental. A recent expert consensus statement recommended using serial amnioinfusions only experimentally as part of research protocols, such as the RAFT trial [1654], as its benefits have not yet been proven.

*28.3.6 **Outcomes postnatally***

There is a scarcity of studies on long-term outcomes after foetal intervention for CLUTO. An SR shows that postnatal renal function between six months and two years appears to be improved in patients after prenatal intervention compared to patients with no intervention [1256, 1263]. After early VAS, patients appear to have higher preservation rates of renal function, even after intermediate follow-up of 4-10 years [1648].

*28.3.7 **Postnatal management***

Details on postnatal diagnostics and management and outcomes can be found in Chapter 21 on the congenital lower urinary tract obstruction.

*28.3.8 **Complex urogenital pathologies - prenatal management and considerations***

- **Megacystis**

Foetal megacystis is defined as an abnormally enlarged foetal bladder if diagnosed in the first trimester when the longitudinal bladder diameter exceeds 7mm and in the second/third trimester when the large and full bladder fails to empty during an extended ultrasound examination. The reported incidence of foetal megacystis is approximately 1 in 1,500-7,000 pregnancies, with a slight male predominance. The condition may represent a transient, self-limiting finding, or be the first manifestation of significant lower urinary tract obstruction (LUTO), chromosomal anomalies or syndromic disorders, thereby influencing prognosis, counselling and management. However, and even in the event of an isolated first-trimester foetal megacystis, completely resolved, the prevalence of chromosomal abnormalities was found in 2.4% of the cases, as was found in a large retrospective multicentre study [1655]. Nevertheless, the authors warrant for specialised paediatric follow-up. While posterior urethral valves (PUV) constitute the most common cause of LUTO in male foetuses, not all cases of foetal megacystis are attributable to PUV. Distinction is critical, as megacystis may also arise from non-obstructive aetiologies or other obstructive mechanisms (e.g. urethral atresia, prune belly syndrome). Therefore, careful differentiation between isolated megacystis and valve-related bladder outlet obstruction is essential for appropriate prenatal risk stratification and postnatal follow-up. A large bladder, bilateral hydroureteronephrosis and bladder wall thickening are the accurate predictors of LUTO [1639]. The keyhole sign, however, has a low diagnostic performance and a low specificity.

A retrospective study in 53 foetuses with a megacystis and an attempt for treatment via intrauterine vesicoamniotic shunting has concluded that, despite early intervention, no improved rate of normal renal function could be observed, and morbidity and mortality also remained high [1656].

Megacystis can be part of a syndrome known as megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), and the large bladder is characterised as a bladder distention without mechanical obstruction [1608].

- **Bladder exstrophy-epispadias complex**

The bladder exstrophy-epispadias complex (BEEC) is a rare congenital anomaly involving the lower abdominal wall, urinary tract, external genitalia and, in some cases, the gastrointestinal tract. BEEC encompasses epispadias and classic bladder exstrophy. The estimated prevalence is 1:30,000-50,000 live births, with a male predominance. The aetiology is multifactorial, with contributions from genetic factors and early embryonic maldevelopment of the cloacal membrane.

Prenatal diagnosis is increasingly possible and important thanks to prenatal ultrasound and foetal MRI, enabling parental counselling and delivery planning. However, in a recent study of more than 280 children born with BEEC, only 60% had been detected during a foetal ultrasound [1606]. Another large study observing the detection during foetal ultrasound over a 20-year period revealed an increase in detection over the years [1605]. Bladder exstrophy has typical characteristics during foetal ultrasound, such as a nonvisible foetal bladder, a low insertion of the umbilical cord, normal kidney anatomy, normal amount of amniotic fluid, an abnormal pubic diastasis, a low umbilical cord insertion-to-genital tubercle length, and malformation of the external genitalia, and can be detected between the 15th and 33rd week of gestation [1607]. An early detection allows for appropriate parental counselling and time for reflection, and in some cases, termination of pregnancy. It is not always possible during foetal ultrasound to distinguish between BEEC and cloacal exstrophy, which a foetal MRI is able to do.

Despite advances in reconstructive surgery, BEEC has lifelong consequences for urinary continence, sexual function, fertility and quality of life, requiring multidisciplinary long-term follow-up.

- **Prune belly syndrome**

Prune belly syndrome (PBS) is another rare congenital disorder defined by the triad of deficient or absent abdominal wall musculature, bilateral cryptorchidism, and urinary tract dilation. PBS has an incidence of one in 30,000-50,000 live births and shows a male predominance in over 95% of cases [1657]. The clinical spectrum is highly variable, ranging from severe, often lethal presentations with pulmonary hypoplasia and early renal failure, to milder phenotypes compatible with long-term survival but associated with chronic urological morbidity. The prognosis of prune belly syndrome is determined by the degree of renal impairment and associated anomalies. The differential diagnosis from a bladder outlet obstruction, as in LUTO during foetal development, is challenging.

In a study with 45 prune belly syndrome patients observed over a period of 18 years, the diagnosis was made prenatally in 39%, two out of three of whom underwent an intrauterine vesicoamniotic shunt [1609]. The neonatal mortality rate was 27%, most often due to pulmonary complications. The advantage of intrauterine vesicoamniotic shunting is limited.

- **Cystic kidney disease**

Cystic kidney disease in the foetus refers to a heterogeneous group of disorders characterised by the presence of one or multiple renal cysts, which may be unilateral or bilateral, isolated or part of a syndromic condition. The overall incidence is estimated at approximately one in 1,000-2,000 pregnancies, with wide variability depending on the underlying diagnosis. Prenatal detection is typically achieved through routine second-trimester ultrasound, which may reveal hyperechogenic kidneys, loss of corticomedullary differentiation and variable cystic patterns. The main differential diagnoses include multicystic dysplastic kidney (MCDK), autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic kidney disease (ADPKD) and syndromic ciliopathies (e.g. Meckel-Gruber syndrome). The diagnosis relies on detailed sonographic assessment, consideration of associated anomalies and, in selected cases, genetic and parental testing is advised [1658]. Genetic testing is performed in study environment [1659].

Foetal intervention is generally not indicated except in rare situations with severe oligohydramnios and preserved renal function, though evidence remains limited [1610]. Prenatal counselling should address diagnostic uncertainty, potential progression and postnatal implications, with long-term outcome depending largely on the underlying disorder, residual renal function and extra-renal involvement [1660]. In the event

of a unilateral MCKD a contralateral compensatory growth of the kidney seems to be a favourable outcome parameter [1602].

28.3.9 Summary of evidence and recommendations for foetal urology

Summary of evidence	LE
Ultrasound examination in the first and second trimester remain the cornerstone for detection of urinary tract malformations.	1b
Megacystis is defined as a longitudinal bladder diameter of ≥7mm in the first trimester and ≥15mm in the second trimester.	2a
An APD of ≥4mm before 28 weeks and ≥ 7mm after 28 weeks is considered abnormal. An APD >15mm strongly predicts the need for postnatal surgery.	1b
Individual risk stratification regarding the need for antibiotic prophylaxis is warranted in children with risk factors such as ureteral dilatation, circumcision status, being a girl and showing high-grade ANH	4
Early oligo- and especially anhydramnios can compromise pulmonary development and result in pulmonary hypoplasia.	1b
Ultrasound parameters that help differentiate obstructive from nonobstructive pathologies include: megacystis, bladder wall thickening, dilated posterior urethra (keyhole sign), bilateral hydroureteronephrosis and oligo- or anhydramnios.	4
Anhydramnios before 20 weeks' gestation is a strong predictor of pulmonary hypoplasia and of foetal and neonatal death.	2a
VAS for CLUTO has been shown to improve perinatal survival in select patients.	4
Differentiation between isolated megacystis and valve-related bladder outlet obstruction is essential for appropriate prenatal risk stratification and postnatal follow-up.	4

Recommendations	Strength rating
Perform screening ultrasound examination in the first (11-14 weeks) and second (17-22 weeks) trimesters to assess for urinary tract malformations.	Strong
Care for patients with urinary tract malformations in a multidisciplinary team (MDT), including maternal-foetal medicine specialists, clinical geneticists, paediatric urologists and nephrologists, neonatologists, and psychologists.	Strong
Obtain foetal urine for prenatal biochemistries by means of serial vesicocenteses.	Weak
Exclude life-limiting genetic or structural anomalies before considering foetal intervention in congenital lower urinary tract obstruction.	Weak
Consider foetal intervention in a foetus with ultrasonographic signs of obstruction and reduced amniotic fluid in the second trimester.	Weak

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30. CONFLICT OF INTEREST

All members of the Paediatric Urology Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/paediatric-urology/panel.

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