

# EAU Guidelines on Paediatric Urology

C. Radmayr (Chair), G. Bogaert, H.S. Dogan, R. Kočvara,  
J.M. Nijman (Vice-chair), R. Stein, S. Tekgül  
Guidelines Associates: L.A. 't Hoen,  
J. Quaedackers, M.S. Silay, S. Undre



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# 1. INTRODUCTION

## 1.1 Aim

A collaborative working group consisting of members representing the European Society for Paediatric Urology (ESPU) and the European Association of Urology (EAU) has prepared these Guidelines with the aim of increasing the quality of care for children with urological conditions. This Guideline document is limited to a number of common clinical pathologies in paediatric urological practice, as covering the entire field of paediatric urology in a single guideline document is unattainable.

The majority of 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 where 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 many different schools of thought and a huge diversity in management.

Knowledge gained by increasing experience, new technological advances and non-invasive diagnostic screening modalities has had a profound influence on treatment modalities in paediatric urology, a trend that is likely to continue in the years to come.

It must be emphasised that clinical guidelines present the best evidence available to the experts but 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 personal values and preferences/individual circumstances of children and their caregivers into account. Guidelines are not mandates and do not purport to be a legal standard of care.

## 1.2 Panel composition

The EAU-ESPU Paediatric Urology Guidelines Panel consists of an international group of clinicians with particular 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 (Pocket guidelines) is available, both in print and as a App for IOS and Android devices. These are abridged versions which may require consultation together with the full text version. A number of translated versions, alongside several scientific publications in European Urology, the Associations scientific journal are also available [1-3]. All documents can be viewed through the EAU website: <http://uroweb.org/guideline/paediatric-urology/>.

## 1.4 Publication history

The Paediatric Urology Guidelines were first published in 2001 [4]. This 2018 publication includes a number of updated chapters and sections as detailed below.

## 1.5 Summary of changes

The literature for the complete document has been assessed and updated, wherever relevant. Key changes in the 2018 publication:

- Section 3.9 - Day-time lower urinary tract conditions: Both the literature and the text have been revised extensively;
- Section 3.10 - Monosymptomatic enuresis - bedwetting: the literature and the text have been revised extensively;
- Section 3.11 - Management of neurogenic bladder: Both the literature and the text have been revised extensively;
- Section 3.15 - Obstructive pathology of renal duplication: ureterocele and ectopic ureter: The literature has been updated resulting in minor amendments to the text.



### 1.5.1 **New and changed recommendations**

#### 3.9.5 **Recommendations for the management of day-time urinary tract conditions**

<b>Recommendations</b>	<b>LE</b>	<b>Strength rating</b>
Use two day voiding diaries and/or structured questionnaires for objective evaluation of symptoms, voiding drinking habits and response to treatment	2	Strong
Use a stepwise approach, starting with the least invasive treatment in managing day-time lower urinary tract dysfunction (LUTD) in children.	4	Weak
Initially offer urotherapy involving bladder rehabilitation and bowel management.	2	Weak
If bladder bowel dysfunction is present, treat bowel dysfunction first, before treating the lower urinary tract condition.	2	Weak
Use pharmacotherapy (mainly antispasmodics and anticholinergics) as second line therapy in OAB.	1	Strong
Use antibiotic prophylaxis if there are recurrent infections.	2	Weak
Re-evaluate in case of treatment failure; this may consist of (video) urodynamics magnetic resonance imaging of lumbosacral spine and other diagnostic modalities, guiding off-label treatment which should only be offered in highly experienced centres.	3	Weak

#### 3.10.5 **Recommendations for the management of monosymptomatic nocturnal enuresis – bedwetting**

<b>Recommendations</b>	<b>LE</b>	<b>Strength rating</b>
Do not treat children less than five years of age in whom spontaneous cure is likely, but 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.	2	Strong
Use voiding diaries or questionnaires to exclude day-time symptoms.	2	Strong
Perform a urine test to exclude the presence of infection or potential causes such as diabetes insipidus.	2	Strong
Offer supportive measures in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important.	1	Strong
Offer desmopressin in proven night-time polyuria.	1	Strong
Offer alarm treatment in motivated and compliant families.	1	Strong

#### 3.11.6 **Recommendations for the management of neurogenic bladder**

<b>Recommendations</b>	<b>LE</b>	<b>Strength rating</b>
Urodynamic studies should be performed in every patient with spina bifida as well as in every child with high suspicion of a neurogenic bladder to estimate the risk for the upper urinary tract and to evaluate the function of the detrusor and the sphincter.	2	Strong
In all newborns, intermittent catheterisation (IC) should be started soon after birth. In those with a clear underactive sphincter and no overactivity starting IC may be delayed. If IC is delayed, closely monitor babies for urinary tract infections, upper tract changes (US) and lower tract (UD).	3	Strong
Start early anticholinergic medication in the new-borns with suspicion of an overactive detrusor.	2	Strong
The use of suburothelial or intradetrusor injection of onabotulinum toxin A is an alternative and a less invasive option in children who are refractory to anticholinergics in contrast to bladder augmentation.	2	Strong
Treatment of faecal incontinence is important to gain continence and independence. Treatment should be started with mild laxatives, rectal suppositories as well as digital. If not sufficient transanal irrigation is recommended, if not practicable or feasible, a Malone antegrade colonic enema (MACE)/Antegrade continence enema (ACE) stoma should be discussed.	3	Strong

ileal or colonic bladder augmentation is recommended in patients with therapy-resistant overactivity of the detrusor, small capacity and poor compliance, which may cause upper tract damage and incontinence. The risk of surgical and non-surgical complications and consequences outweigh the risk for permanent damage of the upper urinary tract +/- incontinence due to the detrusor.	2	Strong
In patients with a neurogenic bladder and a weak sphincter, a bladder outlet procedure should be offered. It should be done in most patients together with a bladder augmentation.	3	Weak
Creation of a continent cutaneous catheterisable channel should be offered to patients who have difficulties in performing a IC through the urethra.	3	Weak
A life-long follow-up of renal and reservoir function should be available and offered to every patient. Addressing sexuality and fertility starting before/ during puberty should be offered.	3	Weak
Urinary tract infections are common in children with neurogenic bladders, however, only symptomatic UTIs should be treated.	3	Weak

3.15.5 **Recommendations for the management of obstructive pathology of renal duplication± ureterocele and ectopic ureter**

Recommendations			LE	Strength rating
Ureterocele	Diagnosis	Use ultrasound (US), radionuclide studies (mercaptoacetyl triglycine (MAG3)/ dimercaptosuccinic acid (DMSA)), voiding cystourethrography (VCUG), magnetic resonance urography, high-resolution magnetic resonance imaging (MRI), and cystoscopy to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction.	3	Weak
	Treatment	Select treatment based on symptoms, function and reflux as well on surgical and parenteral choices: observation, endoscopic decompression, ureteral re-implantation, partial ephroureterectomy, complete primary reconstruction.	3	Weak
		Offer, early endoscopic decompression to patients with an obstructing ureterocele.		
Ectopic ureter	Diagnosis	Use US, DMSA scan, VCUG or MRI for a definitive diagnosis.	3	Weak
	Treatment	In non-functioning moieties with recurrent infections, heminephro-ureterectomy is a definitive solution. Ureteral reconstruction (ureteral re-implantation/ureteroureterostomy/ ureteropyelostomy and upper-pole ureterectomy) are other therapeutic options, especially in cases in which the upper pole has function worth preserving.	3	Weak

## 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 and 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) - influenced also by the fact that a considerable number of treatment options relate to surgical interventions on a large spectrum of different 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.

For the 2018 edition of the EAU Guidelines, the Guidelines Office have transitioned to a modified GRADE methodology across all 20 guidelines [5, 6]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [7];
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;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [8]. 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 nature and variability of patient values and preferences. The strength rating forms will be made available online.

Additional information can be found in the general Methodology section of this print, and 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.

## 2.3 Future goals

The Paediatric Urology Guidelines Panel aim to systematically address the following key clinical topic in a future update of the Guidelines:

- What are the short-term and long-term benefits and harms of varicocele intervention in children? [9].

# 3. THE GUIDELINE

## 3.1 Phimosis

### 3.1.1 *Epidemiology, aetiology and pathophysiology*

At the end of the first year of life, retraction of the foreskin behind the glandular sulcus is possible in approximately 50% of boys; this rises to approximately 89% by the age of three years. The incidence of phimosis is 8% in six to seven year olds and just 1% in males aged sixteen to eighteen years [10].

### 3.1.2 *Classification systems*

The phimosis is either primary with no sign of scarring, or secondary (pathological) to a scarring such as balanitis xerotica obliterans (BXO) [10]. Balanitis xerotica obliterans, also termed lichen sclerosis, has been recently found in 35% circumcised prepuce in children and adolescents and in 17% of boys younger than ten years presenting with phimosis. The clinical appearance of BXO in children may be confusing and does not correlate with the final histopathological results. Lymphocyte-mediated chronic inflammatory disease was the most common finding [11, 12] (LE: 2b).

Phimosis has to be distinguished from normal agglutination of the foreskin to the glans, which is a more or less lasting physiological phenomenon with clearly-visible meatus and free partial retraction [13]. Separation of the prepuce from the glans is based on accumulated epithelial debris and penile erections. Forceful preputial retraction should be discouraged to avoid cicatrix formation [14].

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

### 3.1.3 **Diagnostic evaluation**

The diagnosis of phimosis and paraphimosis is made by physical examination. If the prepuce is not retractable, or only partly retractable, and shows a constrictive ring on drawing back over the glans penis, a disproportion between the width of the foreskin and the diameter of the glans penis has to be assumed. In addition to the constricted foreskin, there may be adhesions between the inner surface of the prepuce and the glanular epithelium and/or a fraenum breve. Paraphimosis is characterised by a retracted foreskin with the constrictive ring localised at the level of the sulcus, which prevents replacement of the foreskin over the glans.

### 3.1.4 **Management**

Conservative treatment is an option for primary phimosis. The steroid therapies were more effective over placebo and manual stretching [15]. A corticoid ointment or cream (0.05-0.1%) can be administered twice a day over a period of 20-30 days with a success rate of > 90% [16-19] (LE: 1b). A recurrence rate of up to 17% can be expected [20]. This treatment has no side effects and the mean bloodspot cortisol levels are not significantly different from an untreated group of patients [21] (LE: 1b). The hypothalamic pituitary-adrenal axis was not influenced by local corticoid treatment [22]. Agglutination of the foreskin does not respond to steroid treatment [17] (LE: 2).

Operative treatment of phimosis in children is dependent on the caregivers' preferences and can be plastic or radical circumcision after completion of the second year of life. Alternatively, the Shang Ring may be used especially in developing countries [23]. Plastic circumcision has the objective of achieving a wide foreskin circumference with full retractability, while the foreskin is preserved (dorsal incision, partial circumcision, trident preputial plasty) [24]. However, this procedure carries the potential for recurrence of the phimosis [25]. In the same session, adhesions are released and an associated fraenum breve is corrected by fraenulotomy. Meatoplasty is added if necessary.

An absolute indication for circumcision is secondary phimosis. In primary phimosis, recurrent balanoposthitis and recurrent urinary tract infections (UTIs) in patients with urinary tract abnormalities are indications for intervention [26-29] (LE: 2b). Male circumcision significantly reduces the bacterial colonisation of the glans penis with regard to both non-uropathogenic and uropathogenic bacteria [30] (LE: 2b). Simple ballooning of the foreskin during micturition is not a strict indication for circumcision.

Routine neonatal circumcision to prevent penile carcinoma is not indicated. A recent meta-analysis could not find any risk in uncircumcised patients without a history of phimosis [31]. Contraindications for circumcision are: an acute local infection and congenital anomalies of the penis, particularly hypospadias or buried penis, as the foreskin may be required for a reconstructive procedure [32, 33]. Circumcision can be performed in children with coagulopathy with 1-5% suffering complications (bleeding), if haemostatic agents or a diathermic knife are used [34, 35]. Childhood circumcision has an appreciable morbidity and should not be recommended without a medical reason and also taking into account epidemiological and social aspects [36-40] (LE: 1b). Balanitis xerotica obliterans is associated with meatal pathology (stenosis) after circumcision in up to 20% of boys and adjuvant local steroid treatment is advised [12, 41].

Treatment of paraphimosis consists of manual compression of the oedematous tissue with a subsequent attempt to retract the tightened foreskin over the glans penis. Injection of hyaluronidase beneath the narrow band or 20% mannitol may be helpful to release the foreskin [42, 43] (LE: 3-4). If this manoeuvre fails, a dorsal incision of the constrictive ring is required. Depending on the local findings, a circumcision is carried out immediately or can be performed in a second session.

### 3.1.5 **Follow-up**

Any surgery done on the prepuce requires an early follow-up of four to six weeks after surgery.

### 3.1.6 **Summary of evidence and recommendations for the management of phimosis**

Summary of evidence	LE
Treatment for phimosis usually starts after two years of age or according to caregivers' preference.	3
In primary phimosis, conservative treatment with a corticoid ointment or cream is a first line treatment with a success rate of more than 90%.	1b

Recommendations	LE	Strength rating
Offer corticoid ointment or cream to treat primary symptomatic phimosis. Circumcision will also solve the problem.	1b	Strong
Treat primary phimosis in patients with recurrent urinary tract infection and/or with urinary tract abnormalities.	2b	Strong
Circumcise in case of lichen sclerosus or scarred phimosis.	2b	Strong
Treat paraphimosis by manual reposition and proceed to surgery if it fails.	3	Strong
Avoid retraction of asymptomatic praeputial adhesions.	2b	Weak

### 3.2 Management of undescended testes

#### 3.2.1 Background

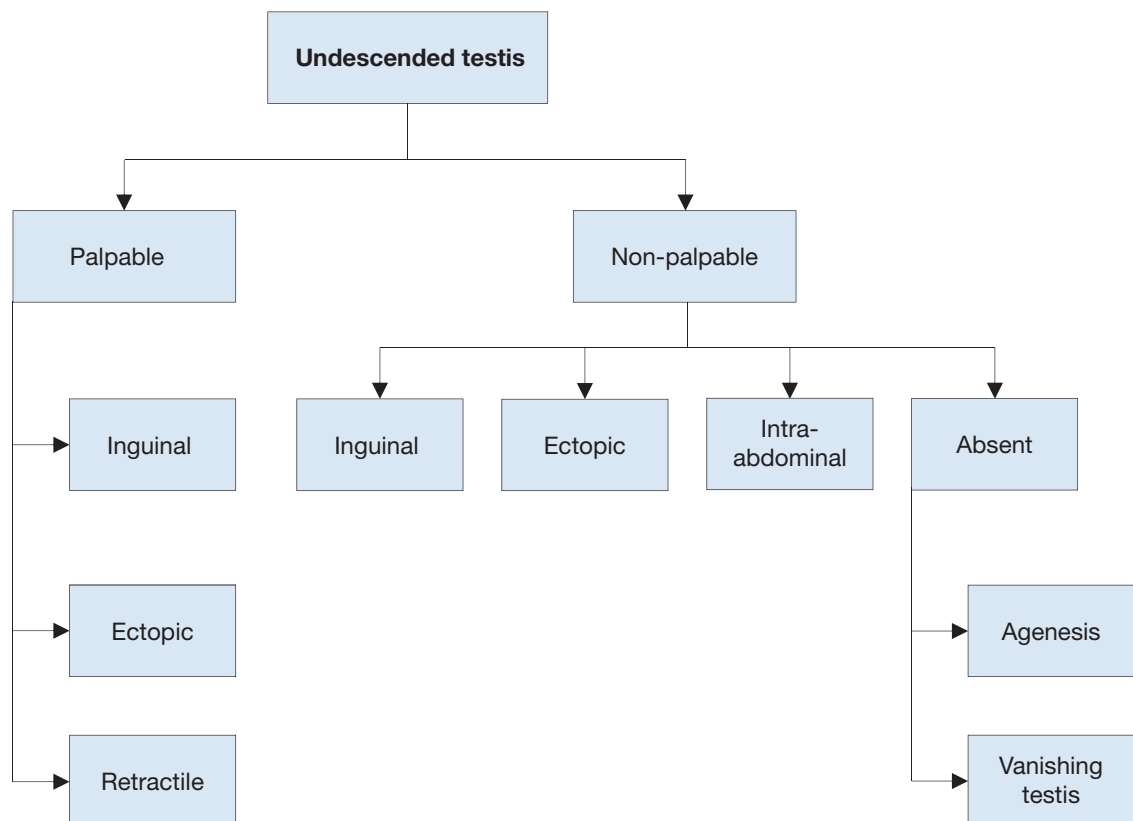
Cryptorchidism or undescended testis is one of the most common congenital malformations of male neonates. Incidence varies and depends on gestational age, affecting 1.0-4.6% of full-term and 1.1-45% of preterm neonates. Following spontaneous descent within the first months of life, nearly 1.0% of all full-term male infants still have undescended testes at one year of age [44]. This congenital malformation may affect both sides in up to 30% of cases [45]. In newborn cases with non-palpable or undescended testes on both sides and any sign of disorders of sex development (DSDs) like concomitant hypospadias, urgent endocrinological and genetic evaluation is required [46].

#### 3.2.2 Classification

The term cryptorchidism is most often used synonymously for undescended testes. The most useful classification of undescended testes is distinguishing into palpable and non-palpable 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 [47]. Acquired undescended testes can be caused by entrapment after herniorrhaphy or spontaneously referred to as ascending testis.

Palpable testes include true undescended testes and ectopic testes. Non-palpable testes include intra-abdominal, inguinal, absent, and sometimes also some ectopic testes. Most importantly, the diagnosis of palpable or non-palpable testis needs to be confirmed once the child is under general anaesthesia, as this is the first step of any surgical procedure for undescended testes.

Figure 1: Classification of undescended testes



### 3.2.2.1 *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 be palpable or not, 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 to be ectopic. The most common aberrant position is in the superficial inguinal pouch. Sometimes 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; therefore, it requires surgical intervention. In addition, an ectopic testis might not be palpable due to its position.

#### *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 [48]. Retractile testes can be easily manipulated down to the scrotum and remain there at least temporarily. They are typically normal in size and consistency. However, they may not be normal and should be monitored carefully since up to one-third can ascend and become undescended [49].

### 3.2.2.2 *Non-palpable testes*

Among the 20% of non-palpable testes, 50-60% are intra-abdominal, canalicular or peeping (right inside the internal inguinal ring). The remaining 20% are absent and 30% are atrophic or rudimentary.

#### *Intra-abdominal testes*

Intra-abdominal testes can be located 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 with the latter one most probably due to an *in utero* infarction of a normal testis by gonadal vessel torsion. The term vanishing testis is commonly used for this condition [50].

### 3.2.3 **Diagnostic evaluation**

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

#### 3.2.3.1 *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 testicular ascent [51]. Prior inguinal surgery is indicative of secondary undescended testes due to entrapment.

#### 3.2.3.2 *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 [52]. A non-palpable testis in the supine position may become palpable once the child is in a sitting or squatting position. If no testis can be identified along the normal path of descent, possible ectopic locations must be considered.

In case of unilateral non-palpable testis, the contralateral testis needs to be examined. Its size and location can have important prognostic implications. Any compensatory hypertrophy suggests testicular absence or atrophy [53]. Nevertheless, this does not preclude surgical exploration since the sign of compensatory hypertrophy is not specific enough [54].

In case of bilateral undescended testes and any evidence or sign of DSDs, such as genital ambiguity, or scrotal hyperpigmentation, further evaluation including endocrinological and genetic assessment becomes mandatory [55].

#### 3.2.3.3 *Imaging studies*

Imaging studies cannot determine with certainty that a testis is present or not [56]. Ultrasound (US) lacks the

diagnostic performance to detect the testis confidently or establish the absence of an intra-abdominal testis [57].

Consequently, the use of different imaging modalities, such as US or MRI [58], for undescended testes is limited and only recommended in specific and selected clinical scenarios (e.g., identification of Müllerian structures in cases with suspicion of DSDs) [57].

### 3.2.4 **Management**

Treatment should be started at the age of six months. After that age, undescended testes rarely descend [59]. Any kind of treatment leading to a scrotally positioned testis should be finished by twelve months, or eighteen 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 [60]. 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 [61].

#### 3.2.4.1 *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 [62, 63].

##### 3.2.4.1.1 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% [64]. However, it must be taken into account that almost 20% of these descended testes have the risk of re-ascending later [65]. 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 [62]. Some authors recommend combined hCG-GnRH treatment. Unfortunately, it is poorly documented and the treatment groups were diverse. Some studies reported successful descent in up to 38% of non-responders to monotherapy [66]. The Panel consensus is that endocrine treatment to achieve testicular descent is not recommended (LE: 4).

#### *Human chorionic gonadotropin*

Human chorionic gonadotropin stimulates endogenous testosterone production and is administered by intramuscular injection. Several dose and administration schedules are reported. There is no proven difference between 1.5 IU and weight-based doses up to 3.0 IU every other day for fourteen days [67]. Similar response rates were achieved with 500 IU once weekly and 1.50 IU three times weekly [68]. However, there is evidence that dosing frequency might affect testicular descent rates. Fewer lower dose injections per week for five weeks seem to be superior to one higher dose every seven to ten days for three weeks with regard to testicular descent [69].

#### *Gonadotropin-releasing hormone*

Gonadotropin-releasing hormone analogues (e.g., buserelin and gonadorelin) are available as nasal sprays, thus avoiding painful intramuscular injections. A typical dosage regimen consists of 1.2 mg per day in three divided doses, for four weeks. Success rates are wide ranging, from 9 to 60%, due to multiple treatment strategies and heterogeneous patient populations [70].

##### 3.2.4.1.2 Medical therapy for fertility potential

Hormonal treatment may improve fertility indices [70, 71] and therefore serve as an additional tool to orchidopexy. There is no difference in treatment with GnRH before (neo-adjuvant) or after (adjuvant) surgical orchidolysis and orchidopexy in terms of increasing fertility index, which may be a predictor for fertility later in life [72]. It is still unknown whether this effect on testicular histology persists into adulthood but it has been shown that men who were treated in childhood with buserelin had better semen analyses compared with men who had childhood orchidopexy alone or placebo treatment [71].

It is reported that hCG treatment may be harmful to future spermatogenesis through increased apoptosis of germ cells, including acute inflammatory changes in the testes and reduced testicular volume in adulthood [73].

Identification of specific subgroups of boys with undescended testes who would benefit from such an approach using hormones is difficult. 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 [74]. The consensus of the Panel recommends endocrine treatment with GnRH analogues in a dosage described above for boys with bilateral undescended testes to preserve the fertility potential (LE: 4).

### 3.2.4.2 Surgical therapy

If a testis has not concluded its descent at the age of six months (corrected for gestational age), and since spontaneous testicular descent is unlikely to occur after that age, surgery should be performed within the subsequent year, and by age eighteen months at the latest [60]. In addition, early orchidopexy can be followed by partial catch-up testicular growth, which is not the case in delayed surgery [75]. All these findings recommend performing early orchidopexy between the ages of six and twelve months [59].

#### 3.2.4.2.1 Palpable testes

Surgery for palpable testes includes orchidofunicolysis and orchidopexy, either via an inguinal or scrotal approach. The latter approach is mainly reserved for low-positioned, undescended testes, with the pros and cons of each method being weighed against each other [76].

##### 3.2.4.2.1.1 Inguinal orchidopexy

Inguinal orchidopexy is a widely used technique with a high success rate of up to 92% [77]. 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 needs to be ligated 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 [78]. Any additional pathology has to be taken care of, such as removal of an appendix testis (hydatid of Morgagni). 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 prognostically bad for fertility. Finally, the mobilised testicle needs to be placed in a sub-dartos pouch within the hemi-scrotum without any tension. In case 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, in order to provide a straight course to the scrotum, might be an option [79]. With regard to fixation sutures, if required, they should be made between the tunica vaginalis and the dartos musculature [80]. 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 [81].

##### 3.2.4.2.1.2 Scrotal orchidopexy

Low-positioned, palpable undescended testis can be fixed through a scrotal incision including division of the gubernaculum, and the processus vaginalis needs to be probed to check for patency [82]. Otherwise, fixation in the scrotum is carried out correspondingly to the inguinal approach. In up to 20% of cases, an inguinal incision will be compulsory to correct an associated inguinal hernia [83]. Any testicular or epididymal appendages can be easily identified and removed. A systematic review shows that the overall success rates ranged from 88 to 100%, with rates of recurrence and post-operative testicular atrophy or hypotrophy < 1% [76].

#### 3.2.4.2.2 Non-palpable testes

For non-palpable testes, surgery must clearly determine whether a testis is present or not [84]. If a testis is found, the decision has to be made to remove it or bring it down to the scrotum. 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 above. Otherwise, the easiest and most accurate way to locate an intra-abdominal testis is diagnostic laparoscopy [85]. Subsequent removal or orchidolysis and orchidopexy can be carried out using the same approach to achieve the therapeutic aims [86]. Some tend to start with inguinal surgical exploration, with possible laparoscopy during the procedure [87]. 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 [88].

During laparoscopy for non-palpable 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%) [89].

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 [90]. A peeping testis can be placed down in the scrotum laparoscopically or via an inguinal incision [91]. Placement of an intra-abdominal testis can sometimes be a surgical challenge. Usually, testes lying > 2 cm above the internal inguinal ring may not reach the scrotum without division of the testicular vessels [92]. Under such circumstances, a Fowler-Stephens orchidopexy may be an option [93] (see Figure 2).



Proximal cutting and transection of the testicular vessels, with conservation of the collateral arterial blood supply, via the deferential artery and cremasteric vessels comprise the key features of the Fowler-Stephens procedure. Recently, 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 [94]. Due to the nature of these approaches the testis is at risk of hypotrophy or atrophy if the collateral blood supply is insufficient [95]. The testicular survival rate in the one-stage Fowler-Stephens technique varies between 50 and 60%, with success rates increasing up to 90% for the two-stage procedure [96]. The advantages of two-stage orchidopexy, with the second part done usually six months after the first, are to allow for development of collateral blood supply and to create greater testicular mobility [97]. In addition preservation of the gubernaculum may also decrease the chance of testicular atrophy [98].

An alternative might be microsurgical auto-transplantation, which has a success rate of up to 90%. However, this approach requires skilled and experienced surgeons and is performed in a limited number of centres [99].

### 3.2.4.2.3 Complications of surgical therapy

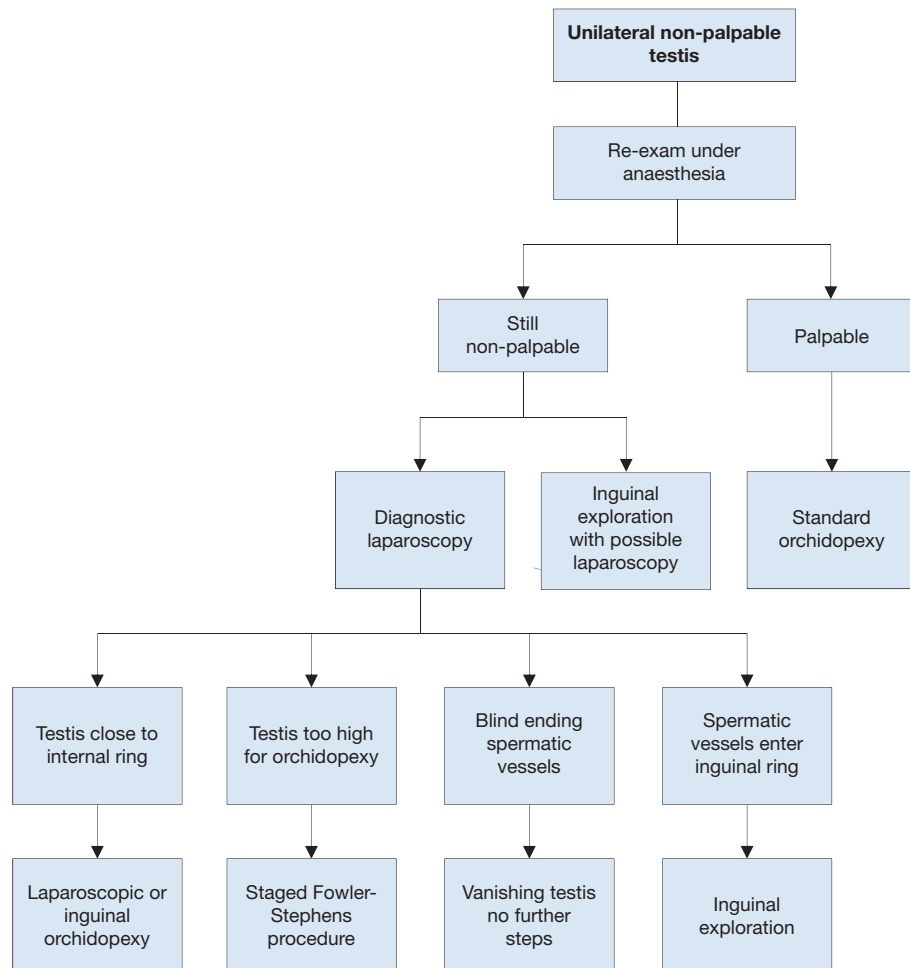
Surgical complications are usually uncommon, with testicular atrophy being the most serious. A systematic review revealed an overall atrophy rate for primary orchidopexy of 1.83%, 28.1% for one-stage Fowler-Stephens procedure, and 8.2% for the two-stage approach [100]. Other rare complications comprise testicular ascent and vas deferens injury besides local wound infection, dehiscence, and haematoma.

### 3.2.4.2.4 Surgical therapy for undescended testes after puberty

A recent study on 51 men diagnosed with inguinal unilateral undescended testis and a normal contralateral one, with no history of any previous therapy, demonstrated a wide range of changes upon histological evaluation. Nearly half of the study population still had significant germ cell activity at different maturation levels. Importantly, the incidence of intratubular germ cell neoplasia was 2% [101].

The Panel consensus recommends orchiectomy in post-pubertal boys with an undescended testis and a normal contralateral one in a scrotal position.

**Figure 2: Treatment of unilateral non-palpable undescended testes**



### 3.2.5 **Undescended testes and fertility**

The association of undescended testes with compromised fertility [102] is extensively discussed in the literature and seems to be a result of multiple factors, including germ cell loss, impaired germ cell maturation [103], Leydig cell diminution and testicular fibrosis [104].

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 of population, whereas paternity reflects the actual potential of fatherhood [105]. 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 age two years compared to individuals who had surgery later, which is indicative of a benefit of earlier orchidopexy [106]. In addition, others demonstrated a relation between undescended testes and increased loss of germ cells and Leydig cells, which is also suggestive of prompt orchidopexy being a significant factor for fertility preservation [107].

Outcome studies for untreated bilateral undescended testes revealed that 100% are oligospermic and 75% azoospermic. Among those successfully treated for bilateral undescended testes, 75% still remain oligospermic and 42% azoospermic [104].

In summary, regarding preservation of fertility potential, early surgical correction of undescended testes is highly recommended before twelve months of age, and by eighteen months at the latest [60].

### 3.2.6 **Undescended testes and malignancy**

Boys who are treated for an undescended testis have an increased risk of developing testicular malignancy. Screening and self-examination both during and after puberty is therefore recommended [108]. A Swedish study, with a cohort of almost 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 thirteen years of age was 2.2 compared to the Swedish general population; this increased to 5.4 for those treated after thirteen years of age [109].

A systematic review and meta-analysis of the literature have also concluded that pre-pubertal orchidopexy may reduce the risk of testicular cancer and that early surgical intervention is indicated in boys with undescended testes [110].

### 3.2.7 **Summary of evidence and recommendations for the management of undescended testes**

<b>Summary of evidence</b>	<b>LE</b>
An undescended testis justifies treatment early in life to avoid loss of spermatogenic potential.	2a
A failed or delayed orchidopexy may increase the risk of testicular malignancy later in life.	2a
The earlier the treatment, the lower the risk 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, fertility and paternity rates are impaired.	1b
The treatment of choice for undescended testis is surgical replacement in the scrotum.	1b
The palpable testis is usually treated surgically using an inguinal approach.	2b
The non-palpable testis is most commonly approached laparoscopically.	2b
There is no consensus on the use of hormonal treatment.	2b

Recommendations	LE	Strength rating
The Panel do not recommend medical or surgical treatment for retractile testes but recommend close follow-up on a yearly basis until puberty.	2a	Strong
Perform surgical orchidolysis and orchidopexy before the age of twelve months, and by eighteen months at the latest.	2b	Strong
Evaluate male neonates with bilateral non-palpable testes for possible disorders of sex development.	1b	Strong
Perform a diagnostic laparoscopy to locate an intra-abdominal testicle.	1a	Strong
Hormonal therapy in unilateral undescended testes is of no benefit for future paternity.	2a	Weak
Offer endocrine treatment in case of bilateral undescended testes.	4	Weak
Inform the patient/caregivers about the increased risk of a later malignancy with an undescended testis in a post-pubertal boy or older and discuss removal in case of a contralateral normal testis in a scrotal position.	3	Weak

### 3.3 Hydrocele

#### 3.3.1 *Epidemiology, aetiology and pathophysiology*

Hydrocele is defined as a collection of fluid between the parietal and visceral layers of the tunica vaginalis [111]. Pathogenesis of primary hydrocele is based on patency of processus vaginalis in contrast with secondary hydrocele. Incomplete obliteration of the processus vaginalis peritonei results in formation of various types of communicating hydrocele; a large open processus vaginalis allowing passage of abdominal viscera results in clinical hernia [112]. The exact time of spontaneous closure of the processus vaginalis is not known. It persists in approximately 80-94% of newborns and in 20% of adults [113]. If complete obliteration of the processus vaginalis occurs with patency of mid-portion, a hydrocele of the cord occurs. Scrotal hydroceles without associated patency of the processus vaginalis are also encountered in newborns [114]. Non-communicating hydroceles, based on an imbalance between the secretion and re-absorption of this fluid, are found secondary to minor trauma, testicular torsion, epididymitis, varicocele operation or may appear as a recurrence after primary repair of a communicating or non-communicating hydrocele.

#### 3.3.2 *Diagnostic evaluation*

The classic description of a communicating hydrocele is that of a hydrocele that vacillates in size, and is usually related to ambulation. It may be diagnosed by history and physical investigation. Transillumination of the scrotum provides the diagnosis in the majority of cases, keeping in mind that fluid-filled intestine and some pre-pubertal tumours may transilluminate as well [115, 116]. If the diagnosis is that of a hydrocele, there will be no history of reducibility and no associated symptoms; the swelling is translucent, smooth and usually not tender. If there are any doubts about the character of an intrascrotal mass, scrotal US should be performed and has nearly 100% sensitivity in detecting intrascrotal lesions. Doppler US studies help to distinguish hydroceles from varicocele and testicular torsion, although these conditions may also be accompanied by a hydrocele.

#### 3.3.3 *Management*

In the majority of infants, surgical treatment of hydrocele is not indicated within the first twelve months because of the tendency for spontaneous resolution [117] (LE: 2). Little risk is taken by initial observation as progression to hernia is rare and does not result in incarceration [117]. Early surgery is indicated if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology [118, 119] (LE: 2). Persistence of a simple scrotal hydrocele beyond twelve months of age may be an indication for surgical correction. There is no evidence that this type of hydrocele risks testicular damage. The natural history of hydrocele is poorly documented beyond the age of two years and according to a systematic review there is no good evidence to support current practice. Delaying surgery may reduce the number of procedures necessary without increasing morbidity [120].

The question of contralateral disease should be addressed by both history and physical examination at the time of initial consultation (LE: 2) [121]. In late-onset hydrocele, suggestive of a non-communicating hydrocele, there is a reasonable chance of spontaneous resolution (75%) and expectant management of six to nine months is recommended [122]. In the paediatric age group, the operation consists of ligation of patent processus vaginalis via inguinal incision and the distal stump is left open, whereas in hydrocele of the cord the cystic mass is excised or unroofed [111, 116, 118] (LE: 4). In expert hands, the incidence of testicular damage during hydrocele or inguinal hernia repair is very low (0.3%) (LE: 3). Sclerosing agents should not be used because of the risk of chemical peritonitis in communicating processus vaginalis peritonei [116, 118] (LE: 4). The scrotal approach (Lord or Jaboulay technique) is used in the treatment of a secondary non-communicating hydrocele.

### 3.3.4 Summary of evidence and recommendations for the management of hydrocele

Summary of evidence	LE
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.	2a
In the paediatric age group, an operation would generally involve ligation of the patent processus vaginalis via inguinal incision.	4

Recommendations	LE	Strength rating
In the majority of infants, observe hydrocele for twelve months prior to considering surgical treatment.	2a	Strong
Perform early surgery if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology.	2b	Strong
Perform a scrotal ultrasound in case of doubt about the character of an intrascrotal mass.	4	Strong
Do not use sclerosing agents because of the risk for chemical peritonitis.	4	Strong

## 3.4 Acute scrotum

### 3.4.1 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 [123-128]. 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) [129-141]. Trauma can also be a cause of acute scrotum as it can relate to post-traumatic haematomas, testicular contusion, rupture dislocation or torsion [142-147]. Scrotal fat necrosis has also been reported to be an uncommon cause of mild-to-moderate scrotal pain in pre-pubertal overweight boys after exposure to cold [148].

In this chapter testicular torsion and epididymitis is discussed, 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 testes occurs over a wider age range.

Epididymitis affects two age groups: less than one year and twelve to fifteen years [126, 149, 150]. One study predicted the annual incidence of epididymitis around 1.2 per 1,000 children [151]. Perinatal torsion of the testis most often occurs prenatally. Bilateral torsion comprises 11-21% of all perinatal cases [152]. Most cases are extravaginal in contrast to the usual intravaginal torsion, which occurs during puberty.

### 3.4.2 Diagnostic evaluation

Patients usually present with scrotal pain, except in neonatal torsion. The sudden onset of invalidating pain in combination with vomiting is typical for torsion of the testis or appendix testes [153, 154].

In general, the duration of symptoms is shorter in testicular torsion (69% present within twelve hours) and torsion of the appendix testes (62%) compared to epididymitis (31%) [125, 126, 150].

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 [150].

An abnormal (horizontal) position of the testis is more frequent in testicular torsion than epididymitis [125]. Looking for absence of the cremasteric reflex is a simple method with 100% sensitivity and 66% specificity for testicular torsion [149, 154] (LE: 3). Elevation of the scrotum may reduce complaints in epididymitis, but not in testicular torsion.

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 [124, 125, 149, 155]. In many cases, it is not easy to determine the cause of acute scrotum based on history and physical examination alone [123-128, 149, 155].

A positive urine culture is only found in a few patients with epididymitis [127, 149, 155, 156]. It should be remembered that a normal urinalysis does not exclude epididymitis. Similarly, an abnormal urinalysis does not exclude testicular torsion.

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% [157-162] (LE: 3). 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 pre-pubertal patients [159, 163]. 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 [159]. A comparison with the other side should always be done.

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% [159, 164] (LE: 2).

Scintigraphy and, more recently, dynamic contrast-enhanced subtraction MRI of the scrotum also provide a comparable sensitivity and specificity to US [165-168]. These investigations may be used when diagnosis is less likely and if torsion of the testis still cannot be excluded from history and physical examination. This should be done without inordinate delays for emergency intervention [155].

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 [169]. Pre-pubertal boys with acute epididymitis have an incidence of underlying urogenital anomalies of 25-27.6%. Complete urological evaluation in all children with acute epididymitis is still debatable [127, 149, 151].

### 3.4.3 **Management**

#### 3.4.3.1 *Epididymitis*

In pre-pubertal 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 [151, 170]. Epididymitis is usually self-limiting and with supportive therapy (i.e. minimal physical activity and analgesics) heals without any sequelae (LE: 3). However, bacterial epididymitis can be complicated by abscess or necrotic testis and surgical exploration is required [171].

#### 3.4.3.2 *Testicular torsion*

Manual detorsion of the testis is done without anaesthesia. It should initially be done by outwards rotation of the testis unless the pain increases or if there is obvious resistance. Success is defined as the immediate relief of all symptoms and normal findings at physical examination [172] (LE: 3). Doppler US may be used for guidance [173]. Bilateral orchiopexy is still required after successful detorsion. This should not be done as an elective procedure, but rather immediately following detorsion. One study reported residual torsion during exploration in 17 out of 53 patients, including eleven patients who had reported pain relief after manual detorsion [172, 174].

Torsion of the appendix testis can be managed non-operatively with the use of anti-inflammatory analgesics (LE: 4). 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 [162].

#### 3.4.3.3 *Surgical treatment*

Testicular torsion is an urgent condition, which requires prompt surgical treatment. The two most important determinants of early salvage rate of the testis are the time between onset of symptoms and detorsion, and the degree of cord twisting [175]. Severe testicular atrophy occurred after torsion for as little as four hours when the turn was  $> 360^\circ$ . In cases of incomplete torsion ( $180-360^\circ$ ), with symptom duration up to twelve hours, no atrophy was observed. However, an absent or severely atrophied testis was found in all cases of torsion  $> 360^\circ$  and symptom duration  $> 24$  hours [176].

Early surgical intervention with detorsion (mean torsion time less than thirteen hours) was found to preserve fertility [177]. Urgent surgical exploration is mandatory in all cases of testicular torsion within 24 hours of symptom onset. In patients with testicular torsion  $> 24$  hours, semi-elective exploration is necessary [175, 176] (LE: 3). There is still controversy on whether to carry out detorsion and to preserve the ipsilateral testis, or to perform an orchiectomy, in order to preserve contralateral function and fertility after testicular torsion of long duration ( $> 24$  hours).

A study found that sperm quality was preserved after orchiectomy and orchidopexy in comparison to normal control men, although orchiectomy resulted in better sperm morphology [178].

During exploration, fixation of the contralateral testis is also performed. Recurrence after orchidopexy is rare (4.5%) and may occur several years later. There is no consensus recommendation about the preferred type of fixation and suture material [179]. Incision of the tunica albuginea with tunica vaginalis graft to prevent or treat compartment syndrome has also been suggested [180].

External cooling before exploration and several medical treatments seem effective in reducing ischaemia-reperfusion injury and preserving the viability of the torsed and the contralateral testis [181-185]. It is good clinical practice to also perform fixation of the contralateral testis in prenatal and neonatal torsion, (although there is no literature to support this) and to remove an atrophied testicle.

#### 3.4.4 **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 [186].

##### 3.4.4.1 *Fertility*

The results vary and are conflicting. In one study, unilateral torsion of the testis seriously intervened with subsequent spermatogenesis in about 50% of the patients and produced borderline impairment in another 20% [167]. Although, 30% of affected testicles with mumps orchitis show a degree of atrophy, long-term outcome in terms of fertility is not conclusive [187].

A recent study showed a normal pregnancy rate after unilateral testicular torsion, with no difference between the patients undergoing orchidopexy and those after orchidectomy [188].

##### 3.4.4.2 *Subfertility*

Subfertility is found in 36-39% of patients after torsion. Semen analysis may be normal in only 5-50% in long-term follow-up [175]. Early surgical intervention (mean torsion time less than thirteen hours) with detorsion was found to preserve fertility, but a prolonged torsion period (mean 70 hours) followed by orchiectomy jeopardised fertility [177].

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 post-ischaemia-reperfusion injury that is caused after the detorsion when oxygen-derived free radicals are rapidly circulated within the testicular parenchyma [175].

##### 3.4.4.3 *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 [178].

##### 3.4.4.4 *Unanswered questions*

Although testicular torsion is a common problem the mechanism of neonatal and prenatal torsion is still not exactly known, as well as whether fixation of the contralateral testicle in these cases is really necessary. The influence of an atrophied testicle on fertility is also unclear.

#### 3.4.5 **Summary of evidence and recommendations for the management of acute scrotum in children**

Summary of evidence	LE
Diagnosis of testicular torsion is based on presentation and physical exam.	
Doppler US is an effective imaging tool to evaluate acute scrotum and comparable to scintigraphy and dynamic contrast-enhanced subtraction MRI.	2a
Neonates with acute scrotum should be treated as surgical emergencies.	3

Recommendations	LE	Strength rating
Testicular torsion is a paediatric urological emergency and requires immediate treatment.	3	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.	3	Weak
Base the clinical decision on physical examination. The use of Doppler ultrasound to evaluate acute scrotum is useful, but this should not delay the intervention.	2a	Strong
Manage torsion of the appendix testis conservatively. Perform surgical exploration in equivocal cases and in patients with persistent pain.	3	Strong
Perform urgent surgical exploration in all cases of testicular torsion within 24 hours of symptom onset. In prenatal torsion the timing of surgery is usually dictated by clinical findings.	3	Strong

## **3.5 Hypospadias**

### **3.5.1 Epidemiology, aetiology and pathophysiology**

#### **3.5.1.1 Epidemiology**

The total prevalence of hypospadias in Europe is 18.6 new cases per 10,000 births (5.1-36.8) according to the recent EUROCAT registry-based study. This incidence was stable over the period of 2001 to 2010 [189, 190]. The mean worldwide prevalence of hypospadias according to an extended systematic literature review varies: 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. There are conflicting data on the recent trends of prevalence – different trends in Europe and an increasing trend in the USA [191, 192].

#### **3.5.2 Risk factors**

Risk factors associated with hypospadias are likely to be genetic, placental and/or environmental [189, 190] (LE: 2b). Interactions between genetic and environmental factors may help explain non-replication in genetic studies of hypospadias. Single nucleotide polymorphisms seemed to influence hypospadias risk only in exposed cases [190, 193] (LE: 2b).

- An additional family member with hypospadias is found in 7% of families, but this is more predominant in anterior and middle forms [193-196].
- Endocrine disorders can be detected in rare cases.
- Babies with a low birth weight have a higher risk of hypospadias [193-196].
- Over the last 25 years, a significant increase in the incidence of hypospadias has been found.
- Endocrines disruptors are one component of a multi-factorial model for hypospadias.
- The use of oral contraceptives prior to pregnancy has not been associated with an increased risk of hypospadias in offspring, but their use after conception increased the risk of middle and posterior hypospadias [194-197] (LE: 2a).

#### **3.5.3 Classification systems**

Hypospadias are usually classified based on the anatomical location of the proximally displaced urethral orifice:

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

The pathology may be different after skin release and should be reclassified accordingly. Anatomical location of meatus may not always be enough to explain the severity and the complex nature of this pathology. Therefore, a simple classification related to severity of the problem, which takes into account penile length, glans size, shape, urethral plate quality and penile curvature is commonly used. In that classification there are two types: mild hypospadias (glanular or penile isolated hypospadias without associated chordee, micropenis or scrotal anomaly);

- severe hypospadias (penoscrotal, perineal hypospadias with associated chordee and scrotal anomalies).

#### **3.5.4 Diagnostic evaluation**

Most hypospadias patients are easily diagnosed at birth (except for the megameatus intact prepuce variant). Diagnosis includes a description of the local findings:

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

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

- cryptorchidism (in up to 10% of cases of hypospadias);
- open processus vaginalis or inguinal hernia (in 9-15%).

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

Urine trickling and ballooning of the urethra requires exclusion of meatal stenosis. The relationship between the severity of the hypospadias and associated anomalies of the upper- or lower urinary tract were not confirmed [198] (LE: 3).

### 3.5.5 **Management**

#### 3.5.5.1 *Indication for reconstruction and therapeutic objectives*

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

The functional indications for surgery are:

- proximally located (ectopic) meatus;
- ventrally deflected or spraying urinary stream;
- meatal stenosis;
- curved penis.

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

- abnormally located meatus;
- cleft glans;
- rotated penis with abnormal cutaneous raphe;
- preputial hood;
- penoscrotal transposition;
- split scrotum.

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

To achieve an overall acceptable functional and cosmetic outcome, the penile curvature must be corrected and a neo-urethra of an adequate size with opening on the glans formed with proper skin coverage of the penile shaft [199] (LE: 4) (Figure 3). The use of magnifying spectacles 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 post-operative treatment are essential for a satisfactory outcome.

#### 3.5.5.2 *Pre-operative hormonal treatment*

Pre-operative hormonal treatment with local or parenteral application of testosterone, dihydrotestosterone or beta-chorionic gonadotropin is usually limited to patients with proximal hypospadias, a small appearing penis, reduced glans circumference or reduced urethral plate [197, 200, 201]. It leads to significant enlargement of the glans and shaft of the penis (LE: 1b).

Moderate quality evidence from three randomised studies demonstrate significantly lower rates of urethra-cutaneous fistulae and reoperation rates in patients who received pre-operative hormonal treatment [202].

Pre-operative testosterone administration is most often well tolerated. Transient side effects on child's behaviour, increased genital pigmentation, appearance of pubic hair, penile skin irritation and redness, increased erections and peri-operative bleeding have been reported, but no persistent side effects related to hormonal stimulation have been reported in the literature. There is also no evidence about possible effects on bone maturation [201-203].

#### 3.5.5.3 *Age at surgery*

The age at surgery for primary hypospadias repair is usually 6-18 (24) months [199, 204, 205] (LE: 3). Age at surgery is not a risk factor for urethroplasty complication in pre-pubertal tubularised incised plate urethroplasty (TIP) repair [204] (LE: 2b). Complication rate after primary TIP repair was 2.5 times higher in adults than in the paediatric group according to a recent prospective controlled study [206] (LE:2a).

#### 3.5.5.4 *Penile curvature*

If present, penile curvature is often released by degloving the penis (skin chordee) and by excision of the connective tissue of the genuine chordee on the ventral aspect of the penis in up to 70% [207]. The urethral plate has well vascularised connective tissue and does not cause curvature in most cases [208, 209]. The residual curvature is caused by corporeal disproportion and requires straightening of the penis, mostly using dorsal midline plication or orthoplasty (modification of the Nesbit plication with or without elevation of the neurovascular bundle). In more severe curvature ( $> 45^\circ$ ), which is often combined with a short urethral plate requiring transection, ventral penile lengthening is recommended to prevent shortening of the penis. This consists of a ventral transverse incision of tunica albuginea extending from the 3 to 9 o'clock position patched with tunica vaginalis flap or graft, or in several short ventral corporotomies without grafting (LE: 2b) [210]. After the ventral lengthening, a shorter dorsal midline plication is usually added.

According to a retrospective study, dorsal plication remained significantly associated with recurrent



ventral curvature independently of the other factors. Ventral corporeal grafting for severe penile curvature gives good long-term results and safety profiles for erectile function [211] (LE: 2b).

#### 3.5.5.5 *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 [209]. Mobilisation of the corpus spongiosum/urethral plate and the bulbar urethra decreases the need for urethral plate transection [210] (LE: 2b).

If the urethral plate is wide, it can be tubularised following the Thiersch-Duplay technique. If the plate is too narrow to be simply tubularised, it is recommended relaxing the plate by a midline incision and its subsequent tubularisation according to the Snodgrass-Orkiszewski TIP technique. This technique has become the treatment of choice in distal and mid-penile hypospadias [212-216]. If the incision of the plate is deep, it is recommended covering the raw surface with inner preputial (or buccal) inlay graft in primary and secondary repairs [217]. This also enables extension of the incision beyond the end of the plate to prevent meatal stenosis [218, 219] (LE 2a).

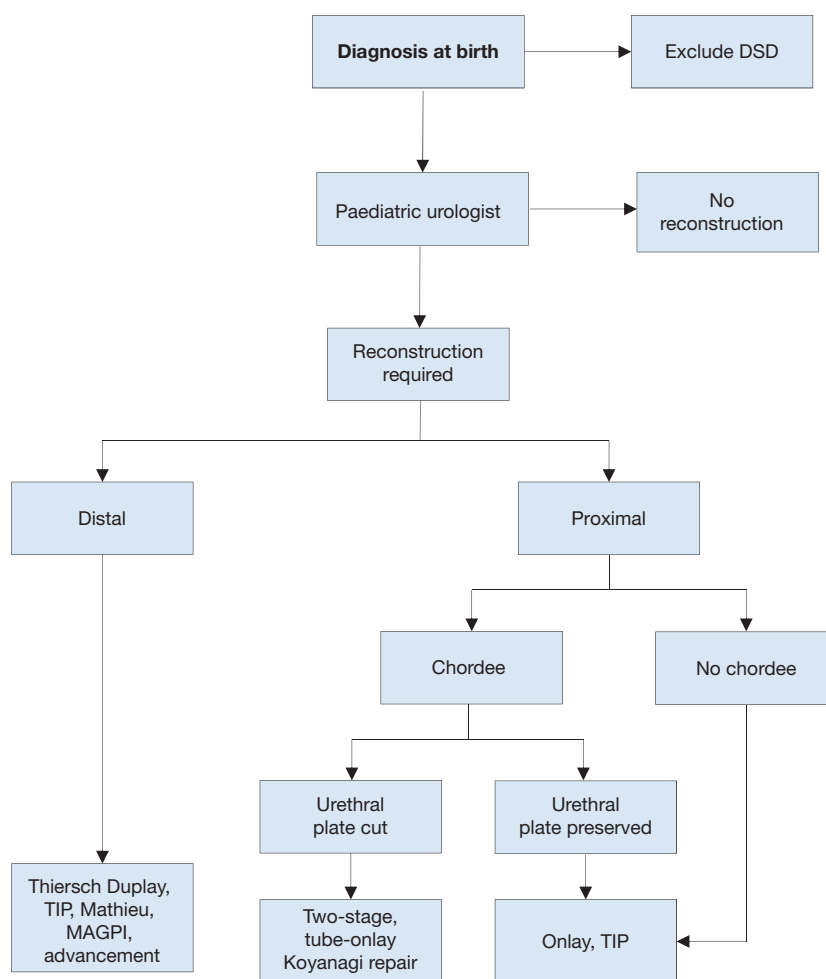
For distal forms of hypospadias, a range of other techniques is available (e.g. Mathieu, urethral advancement) [220] (LE: 2b). The TIP technique has become an option for proximal hypospadias as well [212-216]. However, urethral plate elevation and urethral mobilisation should not be combined with TIP repair because it results in focal devascularisation of the neo-urethra with symptomatic stricture development [221] (LE: 2b). The onlay technique using a preputial island flap is a standard repair, preferred in proximal hypospadias, if a plate is unhealthy or too narrow [207]. An onlay preputial graft is an option for single-stage repair [222] (LE: 2b).

If the continuity of the urethral plate cannot be preserved, single or two-stage repairs are used. For the former, a modification of the tubularised flap (Duckett tube), such as a tube-onlay or an inlay-onlay flap, or onlay flap on albuginea are used to prevent urethral stricture [223-225] (LE: 3); alternatively the Koyanagi-Hayashi technique is used [226-229]. The two-stage procedure has become preferable over the past few years because of lower recurrence of ventral curvature and more favourable results with variable long-term complication rate [219, 223, 230-234].

#### 3.5.5.6 *Re-do hypospadias repairs*

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

**Figure 3: Algorithm for the management of hypospadias**



DSD = disorders of sex development; GAP = glans approximation procedure; TIP = tubularised incised plate urethroplasty; MAGPI = meatal advancement and glanuloplasty incorporated.

### 3.5.5.7 Penile reconstruction following formation of the neo-urethra

Following formation of the neo-urethra, the procedure is completed by glansplasty and by reconstruction of the penile skin. If there is a shortage of skin covering, the preputial double-face technique or placement of the suture line into the scrotum according to Cecil-Michalowski is used. In countries where circumcision is not routinely performed, preputial reconstruction can be considered. Preputial reconstruction carries a risk of specific complications but does not seem to increase the risk of urethroplasty complications [235]. In the TIP repair, the use of a preputial dartos flap reduces the fistula rate [212, 213] (LE: 2b).

### 3.5.5.8 Urine drainage and wound dressing

Urine is drained transurethrally (e.g. dripping stent) or with a suprapubic tube. No drainage after distal hypospadias repair is another option [236, 237]. Circular dressing with slight compression, as well as prophylactic antibiotics during surgery, are established procedures [237] (LE: 4). Post-operative prophylaxis after hypospadias repair is controversial [238, 239] (LE: 2b). There is no consensus on duration of stenting and dressing.

### 3.5.5.9 Outcome

Some studies have tried to determine risk factors for complications after hypospadias repair. An analysis of prospectively collected data found glans size (width < 14 mm), proximal meatal location and re-operation as independent risk factors for urethral complication [237, 240]. Low surgeon volume independently increases the risk of fistula, stricture or diverticulum repair [237, 241] (LE: 3).

A meta-analysis of complication rates of TIP repair found lower complication rate and incidence of re-operations in primary distal repairs (in 4.5%) than in primary proximal repairs (in 12.2%) and in secondary

repair (in 23.3%) [212-216, 237]. One should expect a predictable outcome with complication rates below 10% in distal hypospadias (fistula, meatal stenosis, dehiscence, recurrent ventral curvature, and haematoma) [241, 242]. A similar incidence of fistula (3.4-3.6%) can be expected after the Mathieu and TIP repairs of distal hypospadias [215, 243, 244].

The complication rate of TIP and onlay repairs of primary severe hypospadias is similar, 24% and 27%, respectively. It is higher in free graft and in preputial island tube urethroplasty [207]. The complication rate of single-stage Koyanagi and Hayashi modification repairs goes up 61%, according to a comparative study [226, 237]. Staged buccal mucosa graft requires a redo grafting in 13% of patients, after the second stage more than one third of patients have complications, mostly with some degree of graft fibrosis [244, 245]. A recent long-term study on two-stage flap repair showed a complication rate of 68% [237], another study showed a re-operation rate of 28% [219, 237].

### 3.5.6 **Follow-up**

Long-term follow-up is necessary up to adolescence to detect urethral stricture, voiding dysfunctions and recurrent penile curvature, diverticula, glanular dehiscence [246]. Up to half of complications requiring re-operation present after the first year post-operatively [247] (LE: 2b).

Obstructive flow curve is common after hypospadias repair and while most are not clinically significant, long-term follow-up is required [248-251] (LE: 2a). Urine flow is significantly lower in patients after hypospadias surgery, especially in those who had corrected chordee, but without significant association with lower urinary symptoms [252] (LE: 2a).

Objective scoring systems have been developed in order to evaluate the results of hypospadias surgery (HOSE) [253] (LE: 2b) and cosmetic appearance (HOPE-Hypospadias Objective Penile Evaluation) [254] (LE: 2a). The Pediatric Penile Perception Score (PPPS) is a reliable instrument to assess penile self-perception in children after hypospadias repair and for appraisal of the surgical result by caregivers and uninvolved urologists [255] (LE: 2a). The surgeon should admit that cosmetic results were judged more optimistically by surgeons as compared to parents using validated tools [256].

Adolescents and adults, who have undergone hypospadias repair in childhood, have a slightly higher rate of dissatisfaction with penile size, especially proximal hypospadias patients, but their sexual behaviour is not different from that of control groups [257, 258] (LE: 2a-b). Another long-term follow-up of men born with hypospadias revealed, in a controlled study, that these patients are less satisfied with penile cosmetic outcome according to all parameters of the PPPS, there was a difference in penile length (9,7 vs 11.6 cm) and more patients had lower maximum urinary flow; and more prominent results were found in proximal hypospadias vs. controls [237, 259].

According to a systematic review of long-term patient satisfaction with cosmetic outcomes [260]:

- patient perception of penile size does not differ greatly from the norm;
- patients approaching puberty have a more negative perception and are more critical about the cosmetic outcomes of surgery;
- patients report high levels of perception of deformity and social embarrassment.

The majority of identified instruments focused on postoperative cosmetic satisfaction, with only one instrument considering urinary function, and no instruments evaluating sexual function and psychosocial sequelae [261].

### 3.5.7 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 (24) months.	3
The therapeutic objectives are to correct the penile curvature, to form a neo-urethra of an adequate size, to bring the new meatus to the tip of the glans, if possible, and to achieve an overall acceptable cosmetic appearance.	4
Androgen stimulation therapy results in increased penile length and glans circumference.	1B
The complication rate is about 10% in distal and 25% in proximal hypospadias one-stage repairs. Higher and variable rates (between 28 and 68%) can occur in two-stage repairs.	3
Sexual functions are usually well preserved but patients report high levels of perception of deformity and social embarrassment.	2b

Recommendations	Strength rating
At birth, differentiate isolated hypospadias from disorders of sex development which are mostly associated with cryptorchidism or micropenis.	Strong
Counsel caregivers on functional indications for surgery, aesthetically feasible operative procedures (psychological, cosmetic indications) and possible complications.	Strong
In children diagnosed with proximal hypospadias and a small appearing penis, reduced glans circumference or reduced urethral plate, pre-operative hormonal androgen stimulation treatment is an option and the body of evidence to accentuate its harms and benefits is inadequate.	Weak
For distal hypospadias, offer Duplay-Thiersch urethroplasty, original and modified tubularised incised plate urethroplasty; use the onlay urethroplasty or two-stage procedures in more severe hypospadias. A treatment algorithm is presented (Figure 3). Correct significant (> 30 degrees) curvature of the penis.	Weak
Ensure long-term follow-up to detect urethral stricture, voiding dysfunctions and recurrent penile curvature, ejaculation disorder, and to evaluate patient's satisfaction.	Strong
Use validated objective scoring systems to assist in evaluating the functional and cosmetic outcome.	Strong

## 3.6 Congenital penile curvature

### 3.6.1 Epidemiology, aetiology and pathophysiology

Congenital penile curvature presents penile bending of a normally formed penis due to corporal disproportion. The incidence at birth is 0.6% and congenital penile curvature is caused by asymmetry of the cavernous bodies but an orthotopic meatus [262] because of developmental arrest during embryogenesis [263]. On the other hand the incidence of clinically significant congenital penile curvature is much lower, because the extent of the curvature and its associated sexual dysfunction varies widely [264]. Most of the cases are ventral deviations (48%), followed by lateral (24%), dorsal (5%), and a combination of ventral and lateral (23%) [265]. Most ventral curvatures are associated with hypospadias due to chordee or ventral dysplasia of cavernous bodies [266]. Similarly, dorsal curvature is mostly associated with exstrophy/epispadias complex.

Curvature > 30° is considered clinically significant; curvature > 60° may interfere with satisfactory sexual intercourse in adulthood (LE: 4). Minor penile curvature may be the result of ventral penile skin deficiency only and should be distinguished from corporal anomalies. For penile curvature associated with hypospadias or epispadias refer to the relevant chapters.

### 3.6.2 Diagnostic evaluation

Penile curvature is frequently not documented until later in childhood since the penis only appears abnormal when erect. Patients are usually concerned with the aesthetic and/or functional aspects of their penis [267]. Besides exact history taking to exclude any possibility of acquired penile curvature (e.g. post-traumatic) a thorough clinical examination is mandatory. In addition, photo documentation of the erect penis clearly showing the curvature from different angles serves as a pre-requisite in pre-operative evaluation [268]. The exact degree of curvature is generally determined at the time of surgery using an artificial erection test.

### 3.6.3 Management

The treatment is surgical, starting with an artificial erection to determine the degree of curvature and to check symmetry after the repair [269]. The ultimate goal of any surgical method used to correct the curvature

is to achieve corpora of similar size. Various procedures are in use ranging from rather simple de-gloving and plication procedures, to corporal rotation, use of free dermal or tunica vaginalis grafts, to complete penile disassembly techniques [270, 271]. Reviews comparing the outcome of Nesbit/modified Nesbit procedures [272] to plication procedures [273] were able to demonstrate that while there is a decreased risk of complications and loss of sensation, it remains unclear whether plication techniques can lead to increased risk of recurrence [274]. Altogether these methods include the risk of post-operative shortening of the penis with an average loss of 2.5 cm in stretched penile length depending on the pre-operative degree of curvature and the type of repair used [275, 276].

Recently the non-corporotomy technique has been introduced with promising results enabling correction of any degree of ventral curvature with neither shortening of the penis nor the risk of post-operative erectile dysfunction [277].

### 3.6.4 **Summary of evidence and recommendations for the management of congenital penile curvature**

Summary of evidence	LE
Isolated congenital penile curvature is relatively uncommon.	2a
Congenital penile curvature is often associated with hypospadias.	2a
Diagnosis is usually made late in childhood.	2a
The penis only appears abnormal when erect.	1b
Congenital penile curvature can cause aesthetic as well as functional sexual problems.	1b
Congenital penile curvature is treated with surgery.	1b
The goal of surgery is to achieve corpora of similar size.	1b

Recommendations	LE	Strength rating
Ensure that a thorough medical history is taken and a full clinical examination done to rule out associated anomalies in boys presenting with congenital curvature.	1a	Strong
Provide photo documentation of the erect penis from different angles as a prerequisite in the pre-operative evaluation.	1b	Strong
Perform surgery after weighing aesthetic as well as functional implications of the curvature.	2b	Weak
At the beginning as well as at the end of surgery, perform artificial erection tests.	2a	Strong

## 3.7 **Varicocele in children and adolescents**

### 3.7.1 **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 beginning of puberty. It 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; they are usually noted only when bilateral varicoceles are present and seldom occur as an isolated finding [278-280].

Varicocele develops during accelerated body growth and increased blood flow to the testes, by a mechanism that is not clearly understood. Genetic factors may be present. An anatomic abnormality leading to impaired venous drainage is expressed by the considerable prevalence of the left side condition where the internal spermatic vein drains into the renal vein. Varicocele can induce apoptotic pathways because of heat stress, androgen deprivation and accumulation of toxic materials. Severe damage is found in 20% of adolescents affected, with abnormal findings in 46% of affected adolescents. Histological findings are similar in children or adolescents and in infertile men. In 70% of patients with grade II and III varicocele, left testicular volume loss was found.

Several authors reported on reversal of testicular growth after varicolectomy in adolescents [281, 282]. An average proportion of catch-up growth of 76.4% (range: 52.6-93.8%) has been found according to a recent meta-analysis [283] (LE: 2a). However, this may partly be attributable to testicular oedema associated with the division of lymphatic vessels [284] (LE: 2).

In about 20% of adolescents with varicocele, fertility problems will arise [285]. The adverse influence of varicocele increases with time. Improvement in sperm parameters has been demonstrated after adolescent varicolectomy [286-289] (LE: 1).

### 3.7.2 **Classification systems**

Varicocele is classified into 3 grades [290]:

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

### 3.7.3 **Diagnostic evaluation**

Varicocele is mostly asymptomatic, rarely causing pain. It may be 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. The size of both testicles should be evaluated during palpation to detect a smaller testis.

Venous reflux into the plexus pampiniformis is diagnosed using Doppler US colour flow mapping in the supine and upright position [291]. Venous reflux detected on US only is classified as subclinical varicocele. To discriminate testicular hypoplasia, the testicular volume is measured by US examination or by orchidometer. In adolescents, a testis that is smaller by > 2 mL or 20% compared to the other testis is considered to be hypoplastic [292] (LE: 2).

Extension of Wilms tumour into the renal vein and inferior vena cava can cause a secondary varicocele. A renal US should be routinely added in pre-pubertal boys and in isolated right varicocele (LE: 4).

In order 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 [288, 293].

### 3.7.4 **Management**

There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later. Beneficial effect of pubertal screening and treatment for varicocele regarding chance of paternity has been questioned according to a corresponding questionnaire in adult patients [294] (LE: 4). The recommended indication criteria for varicocelectomy in children and adolescents are [279]:

- varicocele associated with a small testis;
- additional testicular condition affecting fertility;
- bilateral palpable varicocele;
- pathological sperm quality (in older adolescents);
- symptomatic varicocele [294].

Testicular (left + right) volume loss in comparison with normal testes is a promising indication criterion, once the normal values are available [295]. 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 (LE: 4).

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

- inguinal (or subinguinal) microsurgical ligation;
- suprainguinal ligation, using open or laparoscopic techniques [296-299].

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

For surgical ligation, some form of optical magnification (microscopic or laparoscopic) should be used because the internal spermatic artery is 0.5 mm in diameter at the level of the internal ring [296, 298]. The recurrence rate is usually < 10%.

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 [284, 296, 297, 300] (LE: 2). The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs, or suprainguinal open or laparoscopic lymphatic-sparing repairs [296, 298, 301, 302]. Intrascrotal application of isosulphan blue was recommended to visualise the lymphatic vessels [303, 304]. In suprainguinal approach, an artery sparing varicocelectomy may not offer any advantage in regards to catch-up growth and is associated with a higher incidence of recurrent varicocele [305, 306].

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 [307, 308]. 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 [279, 307, 308] (LE: 2).

There is low to moderate level of evidence that radiological or surgical treatment of adolescent varicocele is associated with improved testicular size/growth and sperm concentration - based on current available randomised controlled trials. The ultimate effects on fertility and paternity rates are not known [309].

Microsurgical varicocele repair in adolescents with varicocele significantly increases paternity rates and decreases time to conception post-operatively. Patients with varicocele who underwent microsurgical varicocele repair had increased sperm parameters and 3.63 times greater odds of paternity than controls who did not undergo varicocele surgery [310].

### 3.7.5 Summary of evidence and recommendations for the management of varicocele

Summary of evidence	LE
Varicocele becomes more frequent at the beginning of puberty and is found in 14-20% of adolescents. Fertility problems are expected in up to 20% of adolescents with a varicocele.	
Pubertal patients with a left grade II and III varicocele have the left testis smaller in up to 70% of cases; in late adolescence the contralateral right testis also becomes smaller.	1b
After adolescent varicocelectomy, left testis catch-up growth and improvement in sperm parameters has been demonstrated.	1a
There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later.	1b
Division of testicular lymphatics leads to hydrocele in up to 40% and to testicular hypertrophy.	1b

Recommendations	LE	Strength rating
Examine varicocele in the standing position and classify into three grades.	4	Strong
Use scrotal ultrasound to detect venous reflux without Valsalva manoeuvre in the supine and upright position and to discriminate testicular hypoplasia.		Strong
In all pre-pubertal boys with a varicocele and in all isolated right varicoceles perform standard renal ultrasound to exclude a retroperitoneal mass.		Strong
Inform parents and patients and offer surgery for: <ul style="list-style-type: none"> <li>varicocele associated with a persistent small testis (size difference of &gt; 2 mL or 20%);</li> <li>varicocele associated with additional testicular condition affecting fertility (cryptorchidism, history of torsion, trauma);</li> <li>varicocele associated with pathological sperm quality (in older adolescents);</li> <li>symptomatic varicocele.</li> </ul>	2	Weak
Use some form of optical magnification (microscopic or laparoscopic magnification) for surgical ligation.	2	Strong
Use lymphatic-sparing varicocelectomy to prevent hydrocele formation and testicular hypertrophy.	2	Strong

## 3.8 Urinary tract infections in children

### 3.8.1 Epidemiology, aetiology and pathophysiology

Urinary tract infections represent the most common bacterial infection in children [311-313]. In neonates, the symptoms differ in many aspects from those in infants and children. The prevalence is higher; there is a male predominance; infections not caused by *Escherichia coli* are more frequent; and there is a higher risk of urosepsis [314, 315].

The incidence varies depending on age and sex. One meta-analysis showed that 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, who presented with fever [314]. In the first year of life, UTIs are more common in boys (3.7%) than girls (2%). Later, the incidence of UTIs changes to ~3% in pre-pubertal girls and 1% in pre-pubertal boys [314-316].

*E. coli* is found in ~75% of UTIs and is more frequent in community-acquired than nosocomial infections. In the latter, *Klebsiella pneumoniae*, *Enterobacter spp.*, *Enterococcus spp.*, *Pseudomonas spp.* and *Candida spp.* are more frequent than in community-acquired UTIs. Neonatal UTI is frequently complicated by bacteraemia. In a retrospective study, 12.4% of blood cultures from neonates admitted for UTI were positive for bacteraemia [317], however, it is less frequent in community-acquired than in nosocomial UTI [317, 318].

### 3.8.2 **Classification systems**

There are five widely used classification systems according to; the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.

#### 3.8.2.1 *Classification according to site*

Lower urinary tract (cystitis) is an inflammatory condition of the urinary bladder mucosa with general signs and symptoms including infection, dysuria, frequency, urgency, malodorous urine, enuresis, haematuria, and suprapubic pain.

Upper urinary tract (pyelonephritis) is 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. Older children may report cystitis symptoms along with fever/flank pain. Infants and children may have non-specific signs such as poor appetite, failure to thrive, lethargy, irritability, vomiting or diarrhoea.

#### 3.8.2.2 *Classification according to episode*

The first UTI may be a sign of anatomical anomalies that may predispose to complications of UTI and potential renal damage [319]. Anatomical evaluation is recommended (see below). Recurrent infection can be divided into unresolved and persistent infection.

In unresolved infection, initial therapy is inadequate for elimination of bacterial growth in the urinary tract (inadequate therapy, inadequate antimicrobial urinary concentration (poor renal concentration/gastrointestinal malabsorption), and infection involving multiple organisms with differing antimicrobial susceptibilities).

Persistent infection is caused by re-emergence of bacteria from a site within the urinary tract coming from a nidus for persistent infection that cannot be eradicated (e.g. infected stones, non-functioning or poorly functioning kidneys/renal segments, ureteral stumps after nephrectomy, necrotic papillae, urachal cyst, urethral diverticulum, peri-urethral gland, vesicointestinal, rectourethral or vesicovaginal fistulas). The same pathogen is identified in recurrent infections, but episodes of sterile urine may occur during and shortly following antimicrobial treatment.

In re-infection, each episode can be caused by a variety of new infecting organisms, in contrast to bacterial persistence in which the same infecting organism is always isolated. However, the most common general pathogenic species is *E. coli*, which occurs in many different serotypes. Therefore, recurrent *E. coli* UTI does not equate to infection with the same organism.

#### 3.8.2.3 *Classification according to severity*

In simple UTI, children may have only mild pyrexia; are able to take fluids and oral medication; are only slightly or not dehydrated; and have a good expected level of compliance. When a low level of compliance is expected, such children should be managed as those with severe UTI. In severe UTI, infection is related to the presence of fever of > 39°C, the feeling of being ill, persistent vomiting, and moderate or severe dehydration.

#### 3.8.2.4 *Classification according to symptoms*

Asymptomatic bacteriuria indicates attenuation of uropathogenic bacteria by the host, or colonisation of the bladder by non-virulent bacteria that are incapable of activating a symptomatic response (no leukocyturia, no symptoms). Asymptomatic UTI includes leukocyturia but no other symptoms.

Symptomatic UTI, includes irritative voiding symptoms, suprapubic pain (cystitis), fever and malaise (pyelonephritis). Cystitis may represent early recognition of an infection destined to become pyelonephritis, or bacterial growth controlled by a balance of virulence and host response.

#### 3.8.2.5 *Classification according to complicating factors*

In uncomplicated UTI, infection occurs in a patient with a morphologically and functionally normal upper and lower urinary tract, normal renal function and competent immune system. This category includes mostly isolated or recurrent bacterial cystitis and is usually associated with a narrow spectrum of infecting pathogens that are easily eradicated by a short course of oral antimicrobial agents. Patients can be managed on an outpatient basis, with an emphasis on documenting resolution of bacteriuria, followed by elective evaluation for potential anatomical or functional abnormalities of the urinary tract [320].

All neonates, most patients with clinical evidence of pyelonephritis, and all children with known mechanical or functional obstructions of the urinary tract, are considered to have complicated UTI. Mechanical obstruction is commonly due to the presence of posterior urethral valves, strictures or stones, independent of their location. Functional obstruction often results from lower urinary tract dysfunction (LUTD) of either neurogenic or non-neurogenic origin and dilating vesicoureteral reflux (VUR). Patients with complicated UTI require hospitalisation and parenteral antibiotics. Prompt anatomical evaluation of the urinary tract is critical to



exclude the presence of significant abnormalities [321]. If mechanical or functional abnormalities are present, adequate drainage of the infected urinary tract is necessary.

### 3.8.3 **Diagnostic evaluation**

#### 3.8.3.1 *Medical history*

Medical history includes the question of a primary (first) or secondary (recurring) infection; possible malformations of the urinary tract (e.g. pre- or post-natal US screening); prior operation; family history; and whether there is constipation or presence of lower urinary tract symptoms (LUTS).

#### 3.8.3.2 *Clinical signs and symptoms*

Neonates with pyelonephritis or urosepsis can present with non-specific symptoms (failure to thrive, jaundice, hyperexcitability and without fever). Urinary tract infection is the cause of fever in 4.1-7.5% of children who present to a paediatric clinic [322, 323]. Septic shock is unusual, even with very high fever. Signs of a UTI may be vague and unspecific in small children, but later on, when they are more than two years old, frequent voiding, dysuria and suprapubic, abdominal or lumbar pain can be detected.

#### 3.8.3.3 *Physical examination*

Physical examination includes a general examination of the throat, lymph nodes, abdomen (constipation, palpable and painful kidney, or palpable bladder), flank, the back (stigmata of spina bifida or sacral agenesis), genitalia (phimosis, labial adhesion, vulvitis, epididymo-orchitis), and temperature.

#### 3.8.3.4 *Urine sampling, analysis and culture*

Urine sampling has to be performed before any antimicrobial agent is administered. The technique for obtaining urine for urinalysis as well as culture affects the rate of contamination, which influences interpretation of the results. Especially in early infancy, it can be challenging and depends on the mode of urine sampling [324].

##### 3.8.3.4.1 *Urine sampling*

Urine must be collected under defined conditions and investigated as soon as possible to confirm or exclude UTI, especially in children with fever. In neonates, infants and non-toilet-trained children, there are four main methods with varying contamination rates and invasiveness to obtain urine:

(1) Plastic bag attached to the cleaned genitalia: This technique is most often used in daily practice. It is helpful when the culture results are negative. Also, 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 [325]. However, if the genitalia are not cleaned and culture is delayed, a high incidence of false-positive results (85-99%) can be found [326, 327].

(2) Clean-catch urine collection: The infant is placed in the lap of a caregiver or member of the nursing staff, who holds a sterile foil bowl underneath the infant's genitalia. The infant is offered oral fluids and urine collection is awaited [328]. This is time consuming and requires proper instruction of the caregivers. There seems to be a good correlation between the results of urine culture obtained by this method and suprapubic aspiration (SPA), with a false-positive rate of 5% and false-negative rate of 12% [328, 329]; however, the contamination rate is higher compared to SPA [330].

(3) Bladder catheterisation: In female infants and also in neonates, this technique may be an alternative to SPA, at a higher contamination rate [331]. In a prospective study using bladder catheterisation in febrile children aged < 36 months, contamination was defined by multiple pathogens, non-pathogens, or colony counts < 10,000 cfu/mL. True UTI was found in 10% of children and 14% of the cultures were contaminated. Univariate analysis of potential predictors identified age less than six months, difficult catheterisation, and uncircumcised boys. In children less than six months and uncircumcised boys a new, sterile catheter with each repeated attempt at catheterisation may lead to less contamination [332], otherwise SPA should be the method of choice.

(4) Suprapubic bladder aspiration: This is the most sensitive method to obtain an uncontaminated urine sample in this age group [333, 334]. Using US to assess bladder filling, simplifies SPA and improves the diagnostic yield of obtaining a urine specimen from 60% to 97% [333, 334]. Complications are rare and have been reported in only 0.22% of cases, ranging from transient haematuria to bowel perforation [335]. However, bladder puncture causes more pain than catheterisation in infants less than two months old [336].

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 peri-urethral area in girls, the use of clean catch, especially midstream urine, could be an acceptable technique for obtaining urine. After cleaning the urethral meatus and perineum with gauze and liquid soap twice, the risk of contamination was reduced from 23.9% (41/171) to 7.8% (14/171) in a randomised trial [337].

If the clinical situation necessitates, and for differential diagnosis of sepsis, it is most appropriate to obtain an adequate urine sample by catheterisation or SPA [329]. In infants, a bag can only be used if the dipstick is negative, otherwise the urine should be obtained through catheterisation or SPA. This is also recommended in children, who are severely ill and a UTI needs to be excluded or confirmed. Blood sampling is dependent on the clinical situation.

#### 3.8.3.4.2 Urinalysis

There are three methods that are commonly used for urinalysis:

(1) Dipsticks: These are appealing because they provide rapid results, do not require microscopy, and are 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 [329, 338]. However, nitrite is not a very sensitive marker for infants, who empty their bladder frequently, and not all urinary pathogens reduce nitrate to nitrite. The test is helpful when the result is positive, because it is highly specific (i.e. there are few false-positive results) [329, 339].

**Table 1: Sensitivity and specificity of component of urinalysis, alone and in combination [329]\***

Test	Sensitivity (Range), %	Specificity (Range), %
Leukocyte esterase test	83 (67-94)	78 (64-92)
Nitrite test	53 (15-82)	98 (90-100)
Leukocyte esterase or nitrite test positive	93 (90-100)	72 (58-91)
Microscopy, white blood cells	73 (32-100)	81 (45-98)
Microscopy, bacteria	81 (16-99)	83 (11-100)
Leucocyte esterase test, nitrite test or microscopy positive	99.8 (99-100)	70 (60-92)

\*Reproduced with permission from Pediatrics 2011 Sep;128(3):595-610, Copyright© 2011 by the AAP [329].

(2) Microscopy: This is the standard method of assessing pyuria after centrifugation of the urine with a threshold of five white blood cells (WBCs) per high-power field (25 WBC/ $\mu$ L) [335]. In uncentrifuged urine,  $> 10$  WBC/ $\mu$ L has been demonstrated to be sensitive for UTI [340] and this could perform well in clinical situations [341]. However, this is rarely done in an outpatient setting.

(3) Flow imaging analysis technology: This is being used increasingly to classify particles in uncentrifuged urine specimens [342]. The numbers of WBCs, squamous epithelial cells and red cells correlate well with those found by manual methods [329].

#### 3.8.3.4.3 Urine culture

After 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.

It is unclear what represents a significant UTI. In severe UTI,  $> 10^5$  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 [315]. The classical definition of  $> 10^5$  cfu/mL of voided urine is still used to define a significant UTI [343, 344]. The American Academy of Pediatric Guidelines on Urinary Tract Infection suggest that the diagnosis should be based on the basis of the presence of both pyuria and at least  $10^5$  cfu/mL. However, some studies have shown that, in voided specimens,  $< 10^4$  organisms may indicate a significant UTI [345, 346]. If urine is obtained by catheterisation,  $10^3 - 10^5$  cfu/mL is considered to be positive, and any counts obtained after SPA should be considered as significant. Mixed cultures are indicative of contamination.

**Table 2: Criteria for UTI in children (adapted from the EAU Guidelines on Urological Infections [347])**

Urine specimen from suprapubic bladder puncture	Urine specimen from bladder catheterisation	Urine specimen from midstream void
Any number of cfu/mL (at least 10 identical colonies)	$> 10^3 - 10^5$ cfu/mL	$> 10^4$ cfu/mL with symptoms $> 10^5$ cfu/mL without symptoms

Pyuria without bacteriuria (sterile 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*.

### 3.8.3.5 Imaging

#### 3.8.3.5.1 Ultrasound

Renal and bladder US within 24 hours is advised in infants with febrile UTI to exclude obstruction of the upper and lower urinary tract. Abnormal results are found in 15% of cases, and 1-2% have abnormalities that require prompt action (e.g. additional evaluation, referral, or surgery) [329]. In other studies, renal US revealed abnormalities in up to 37% of cases, whereas voiding cystourethrography (VCUG) showed VUR in 27% of cases [318]. Dilating VUR is missed by US in around one third of cases [348]. Post-void residual (PVR) urine should be measured in toilet-trained children to exclude voiding abnormalities as a cause of UTI. Elevated post-void residual urine volume predicts recurrence of UTIs in toilet-trained children [349].

#### 3.8.3.5.2 Radionuclide scanning

Changes in dimercaptosuccinic acid (DMSA) clearance during acute UTI indicate pyelonephritis or parenchymal damage, correlated well with the presence of dilating reflux and the risk of further pyelonephritis episodes, breakthrough infections [350] and future renal scarring. In the acute phase of a febrile UTI (up to four to six weeks), DMSA-scan can demonstrate pyelonephritis by perfusion defects. Renal scars can be detected after three to six months [351]. These findings are different in neonates. After the first symptomatic, community-acquired UTI, the majority of renal units with VUR grade III or higher had normal early DMSA scanning [352]. The average effective radiation dose of a single DMSA scan was 2.84 (1-12) mSv in one study [353]. See also Chapter 3.13 on VUR.

#### 3.8.3.5.3 Voiding cystourethrography

The gold standard to exclude or confirm VUR is VCUG. Due to the risk of renal scarring, VCUG is recommended after the first episode of febrile UTI in boys and girls depending on sex, age and clinical presentation (see Figure 4 and Table 4) (see also Chapter 3.13). The timing of VCUG does not influence the presence or severity of VUR [354, 355]. Performance of early VCUG in patients with proven sterile urine does not cause any significant morbidity [356]. Another option is doing DMSA first, followed by VCUG if there is renal cortical uptake deficiency after UTI (see Chapter 3.13).

### 3.8.3.6 Bladder and bowel dysfunction

Bladder and bowel dysfunction (BBD) are risk factors for which each child with UTI should be screened upon presentation. Normalisation of micturition disorders or bladder over-activity is important to lower the rate of UTI recurrence. If there are signs of BBD at infection-free intervals, further diagnosis and effective treatment are strongly recommended [357-360]. Treatment of constipation leads to a decrease in UTI recurrence [361-363]. Therefore, exclusion of BBD is strongly recommended in any child with febrile and/or recurrent UTI, and it should be treated if there is evidence of BBD.

## 3.8.4 Management

### 3.8.4.1 Administration route

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; non-compliance; 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. Electrolyte disorders with life-threatening hyponatraemia and hyperkalaemia based on pseudohypoaldosteronism can occur in these cases [364, 365].

Parental combination treatment with ampicillin and an aminoglycoside (e.g. tobramycin or gentamicin) or, respectively, a third-generation cephalosporin achieves excellent therapeutic results (high efficacy of aminoglycosides, respectively cephalosporins against common uropathogens; enterococcus gap is closed with ampicillin). Compared to the division in two doses, a daily single dose of aminoglycosides is safe and effective [321, 366, 367].

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 [329]. Not all available antibiotics are approved by the national health authorities, especially in infancy. In uncomplicated nephritis, both oral and parenteral treatment can be considered, because both are equally effective in children without urinary tract abnormalities. Some studies have demonstrated that once daily parenteral administration of gentamicin or ceftriaxone in a day treatment centre is safe, effective and cost-effective in children with UTI [366, 368, 369]. Delaying treatment in children with a febrile UTI for more than 48-72 hours increase the risk of renal scars [370, 371].

#### 3.8.4.2 Duration of therapy

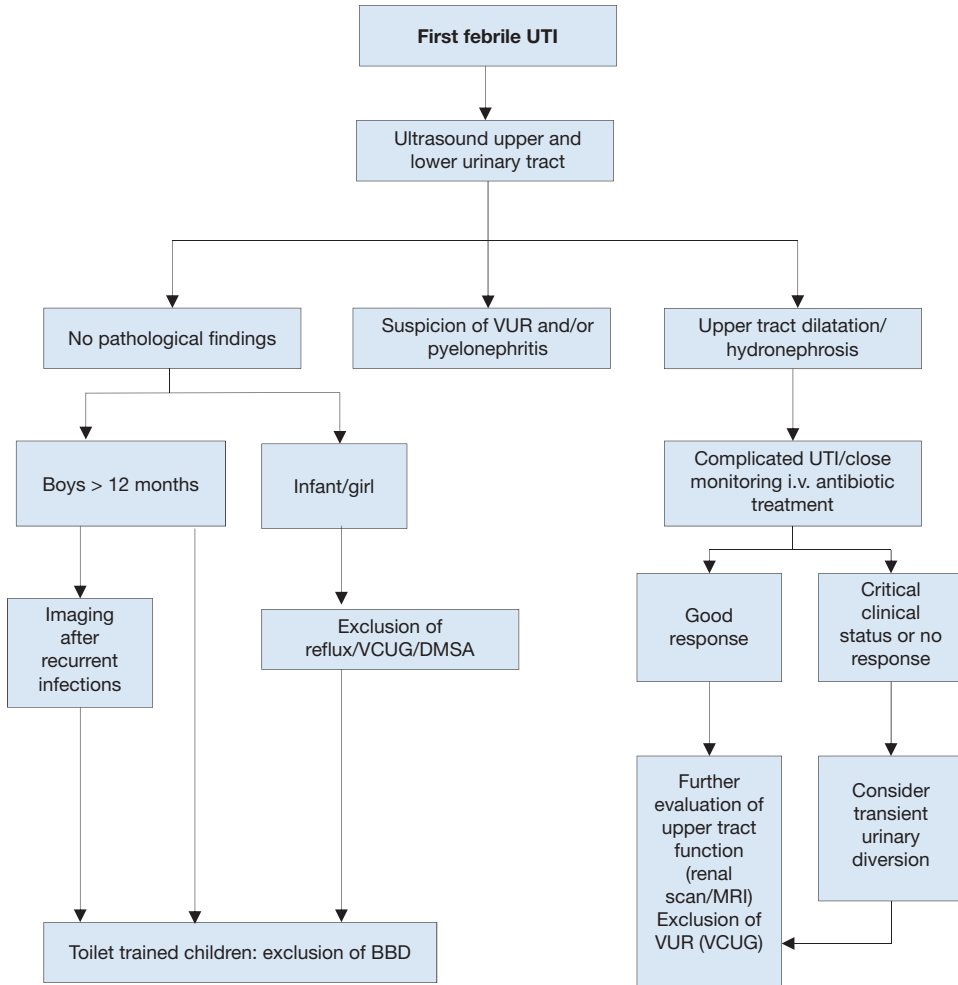
Prompt adequate treatment of UTI can prevent the spread of infection and renal scarring. Outcomes of short courses (one to three days) are inferior to those of seven to fourteen-day courses [329]. In newborns and young infants with a febrile UTI, up to 20% may have a positive blood culture [317, 321]. In late infancy, there are no differences between strategies regarding the incidence of parenchymal scars, as diagnosed with DMSA scan [372]. Some recent studies using exclusively oral therapy with a third-generation cephalosporin (e.g. cefixime or ceftibuten) have demonstrated that this is equivalent to the usual two to four days intravenous therapy followed by oral treatment [367, 373-375]. Similar data have been shown for amoxicillin-clavulanate [376]. If ambulatory therapy is chosen, adequate surveillance, medical supervision and, if necessary, adjustment of therapy must be guaranteed. In the initial phase of therapy, a close ambulant contact to the family is advised [377].

In complicated UTI, uropathogens other than *E. coli*, such as *Proteus mirabilis*, *Klebsiella spp.*, *Pseudomonas aeruginosa*, *enterococci* and *staphylococci* are more often the causative pathogens [321].

Parenteral treatment with broad-spectrum antibiotics is preferred. A temporary urinary diversion (suprapubiccystostomy or percutaneous nephrostomy) might be required in case of failure of conservative treatment in obstructive uropathy. Acute focal bacterial nephritis (lobar nephronia) is a localised bacterial infection of the kidney that presents as an inflammatory mass without abscess formation. This may represent a relatively early stage of renal abscess. For the majority of children, the pathogenesis is related to ascending infection due to pre-existing uropathy, especially vesicorenal reflux or urinary obstruction (mega-ureter).

Prolonged intravenous antibiotic treatment is sufficient in most cases [378], and intravenous and oral therapy tailored to the pathogen identified in culture is recommended [379].

**Figure 4: Algorithm for disease management of first febrile UTI**



*BBD = Bladder Bowel Dysfunction; DMSA = technetium<sup>99</sup>-labelled dimercaptosuccinic acid; MRI = magnetic resonance imaging; UTI = urinary tract infection; VCUG = voiding cystourethrography; VUR = vesicoureteral reflux.*

**3.8.4.3 Antimicrobial agents**

There is a great difference in the prevalence of antibiotic resistance of uropathogenic *E. coli* in different countries, with an alarmingly high resistance in Iran and Vietnam [380]. There are upcoming reports of UTIs caused by extended spectrum  $\beta$ -lactamase-producing enterobacteriaceae (ESBL) in children. In one study from Turkey, 49% of the children less than one year of age and 38% of those more than one year of age had ESBL-producing bacteria that were resistant to trimethoprim/sulfamethoxazole in 83%, to nitrofurantoin in 18%, to quinolones in 47%, and to aminoglycosides in 40% [381]. Fortunately, the outcome appears to be the same as for children with non-ESBL-producing bacteria, despite the fact that initial intravenous empirical antibiotic therapy was inappropriate in one study [382].

**Table 3: Frequently used antibacterial substances for the therapy of urinary tract infections in infants and children\***

Chemotherapeutics	Daily dosage	Application	Comments
<b>Parenteral cephalosporins</b>			
Group 3a, e.g. cefotaxime	100-200 mg/kg (Adolesc.: 3-6 g)	i.v. in 2-3 D	
Group 3b, e.g. ceftazidime	100-150 mg/kg (Adolesc.: 2-6 g)	i.v. in 2-3 D	
Ceftriaxone	75 mg/kg	i.v. in 1 D	
<b>Oral cephalosporins</b>			
Group 3, e.g. ceftibuten	9 mg/kg (Adolesc.: 0.4 g)	p.o. in 1-2 D	
Group 3, e.g. cefixime	8-12 mg/kg (Adolesc.: 0.4 g)	p.o. in 1-2 D	
Group 2, e.g. cefpodoxime proxetil	8-10 mg/kg (Adolesc.: 0.4 g)	p.o. in 2 D	
Group 2, e.g. cefuroximaxetil	20-30 mg/kg (Adolesc.: 0.5-1 g)	p.o. in 3 D	
Group 1, e.g. cefaclor	50 -100 mg/kg (Adolesc.: 1.5-4 g)	p.o. in 2-3 D	
Trimethoprim or Trimethoprim/sulfamethoxazole	5-6 mg/kg 5-6 mg/kg (TMP-Anteil) (Adolesc.: 320 mg)	p.o. in 2 D p.o. in 2 D	
Ampicillin	100-200 mg/kg (Adolesc.: 3-6 g)	i.v. in 3 D	Ampicillin and Amoxicillin are not eligible for calculated therapy
Amoxicillin	50-100 mg/kg (Adolesc.: 1.5-6 g)	i.v. in 3-4 D p.o. in 2-3 D <sup>1</sup>	
Amoxicillin/clavulanic acid (parenteral)	60-100 mg/kg (Adolesc.: 3.6-6.6 g)	p.o. in 2-3 D i.v. in 3 D	
Amoxicillin/clavulanic acid (oral)	45-60 mg/kg (Amoxicillinfraction) (Adolesc.: 1500 + 375 mg)	i.v. in 3 D p.o. in 3 D	
Piperacillin	300 mg/kg	p.o.in 3 D i.v. in 3-4 D	
Tobramycin	5 mg/kg (Adolesc.: 3-5 mg/ kg, max. 0.4 g)	i.v. in 1 D	
Gentamicin	5 mg/kg (Adolesc.: 3-5 mg/ kg, max. 0.4g)	i.v. in 1 D	
Ciprofloxacin	Children and adolesc. (1-17 years of age): 20-30 mg/kg (max. D: 400 mg) (parenterally)	i.v. in 3 D	Approved in most European countries as second- or third line medication for complicated UTIs, "reserve-antibiotic"!
	Children and adolesc. (1-17 years of age): 20-40 mg/kg (max. D 750 mg) (orally)	p.o. in 2 D	
Nitrofurantoin	3-5 mg	p.o. in 2 D	Contraindicated in the case of renal insufficiency

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Dosage for adolescents in paracentesis, if differing. 1 Infants 2 D, children 1-12 ys. 3 D.

i.v. = intravenous; p.o. = by mouth.

**Table 4: Recommendations for calculated antibacterial therapy of pyelonephritis dependent on age and severity of the infection\***

Diagnosis	Proposal	Application	Duration of therapy	LE
Pyelonephritis during the first 0-6 months of life	Ceftazidime + Ampicillin <sup>1</sup> or Aminoglycoside + Ampicillin <sup>1</sup>	3-7 D parenterally, for at least 2 D after defervescence, then oral therapy <sup>2</sup> In newborns: parenteral therapy for 7-14 D, then oral therapy <sup>2</sup>	10 (-14) D Newborns 14-21 D	4
Uncomplicated pyelonephritis after 6 months of age	Cephalosporin group 3 <sup>2</sup>	Orally (initially parenterally, if necessary)	(7-)-10 D	1
Complicated pyelonephritis/ urosepsis (all ages)	Ceftazidime + Ampicillin <sup>1</sup> or Aminoglycoside + Ampicillin <sup>1</sup>	7 D parenterally, then oral therapy <sup>2</sup>	10-14 D	4

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1 after receipt of microbiological findings (pathogen, resistance) adaptation of therapy.

2 i.v.: e.g. cefotaxime; orally: e.g. cefpodoxime proxetil, ceftibuten, cefixime.

**Table 5: Frequently used antibacterial agents used for the treatment of cystitis and cystourethritis (Dosages for children up to twelve years of age)\***

Chemotherapeutics	Daily dosage	Application
Oral cephalosporins		
Group 1, e.g. cefaclor	50 (-100) mg/kgbw	p.o. in 2-3 D
Group 1, e.g. cefalexin	50 mg/kgbw	p.o. in 3-4 D
Group 2, e.g. cefuroximaxetil	20-30 mg/kgbw	p.o. in 2 D
Group 2, e.g. cefpodoxime proxetil	8-10 mg/kgbw	p.o. in 2 D
Group 3, e.g. ceftibuten	9 mg/kgbw	p.o. in 1 D
Trimethoprim	5-6 mg/kgbw	p.o. in 2 D
Trimethoprim/sulfamethoxazole	5-6 mg/kgbw (TMP-fraction)	p.o. in 3 D
Amoxicillin/clavulanic acid	37.5-75 mg/kgbw (Amoxicillin-fraction)	p.o. in 3 D
Nitrofurantoin	3-5 mg/kgbw	p.o. in 2 D

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#### 3.8.4.4 Chemoprophylaxis

Long-term antibacterial prophylaxis should be considered in cases of high susceptibility to UTI and risk of acquired renal damage. Some recently published prospective, randomised studies do not support the efficacy of antibacterial prophylaxis [384-387]. However, two recently published prospective randomised trials as well as one meta-analysis demonstrated a significant risk reduction of developing another UTI by using continuous antibiotic prophylaxis [373, 388, 389] (see also Chapter 3.13 on VUR).

Cranberry juice as well as probiotics may also prevent recurrence of UTI as demonstrated by RCTs [390-392]. A Cochrane review could not rule out some benefit of using probiotics [393].

**Table 6: Drugs for antibacterial prophylaxis\***

Substance	Prophylactic dosage (mg/kg bw/d)	Limitations in neonates and infants
Trimethoprim**	1	Until six weeks of age
Trimethoprim Sulfamethoxazole	1-2 10-15	Not recommended under two months of age
Nitrofurantoin**	1	Until three months of age
Cefaclor	10	No age limitations
Cefixim	2	Preterms and newborns
Ceftibuten	2	***
Cefuroximaxetil	5	***

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

\*\*\* In Germany, ceftibuten is not approved for infants < 3 months old.

#### 3.8.4.5 Monitoring of UTI

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 24-48 hours after the start of therapy in 90% of cases. In patients with prolonged fever and failing recovery, treatment-resistant uropathogens or the presence of congenital uropathy or acute urinary obstruction should be considered. Immediate US examination is recommended in these cases.

Procalcitonin (among other laboratory inflammatory parameters such as C-reactive protein and leukocyte count) can be used as reliable serum marker for early prediction of renal parenchymal inflammation with first febrile UTI [394]. In patients with febrile UTI, serum electrolytes and blood cell counts should be obtained.

#### 3.8.5 Summary of evidence and recommendations for the management of UTI in children

Summary of evidence	LE
Urinary tract infection represents the most common bacterial infection in children less than 2 years of age. The incidence varies depending on age and sex.	1b
Classifications are made according to the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.	2b
The number of colony forming units (cfu) in the urine culture can vary and is related to the method of specimen collection, diuresis, and time and temperature of storage until cultivation occurs.	2b
The classical definition of > 10 <sup>5</sup> cfu/mL in voided urine is still used to define a significant UTI.	3
Changes in DMSA clearance during acute UTI indicate pyelonephritis or parenchymal damage. If it is positive, reflux may be present.	2a



Recommendations	LE	Strength rating
Take a medical history, assess clinical signs and symptoms and perform a physical examination to diagnose children suspected of having a urinary tract infection (UTI).	3	Strong
Exclude bladder- and bowel dysfunction in any child with febrile and/or recurrent UTI and do not delay diagnosis and treatment of bladder-bowel-dysfunction.	3	Strong
The most effective way to collect an uncontaminated urine sample in an infant is through suprapubic bladder aspiration, bladder catheterisation is an alternative with a higher contamination rate.	2a	Strong
Do not use plastic bags for urine sampling in non-toilet-trained children since it has a high risk of false-positive results. Clean catch urine is an acceptable technique for toilet-trained children.	2a	Strong
Urinalysis by dipstick yields rapid results, but it should be used with caution. Microscopic investigation is the standard method of assessing pyuria after centrifugation. Using flow imaging analysis, the numbers of white blood cells (WBCs), squamous epithelial cells and red cells correlate well with manual methods.	2a	Weak
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; non-compliance; complicated pyelonephritis.	2a	Strong
Treat UTIs with four to seven day courses of oral or parenteral therapy.	1b	Strong
Offer long-term antibacterial prophylaxis in case of high susceptibility to UTI and risk of acquired renal damage and lower urinary tract symptoms.	1b	Weak
Treat complicated UTI, with broad-spectrum antibiotics (parenteral).	1b	Weak
In infants with febrile UTI, use renal and bladder ultrasound to exclude obstruction of the upper and lower urinary tract.	3	Strong
In all infants, exclude vesicoureteral reflux (VUR) after the first episode of febrile UTI, using voiding cystourethrography (VCUG) or a dimercaptosuccinic acid (DMSA) scan first (in case of a positive DMSA-scan, follow-up with VCUG). In boys more than one year of age, exclude VUR after the second febrile UTI.	2a	Strong

### 3.9 Day-time lower urinary tract conditions

#### 3.9.1 Terminology, classification, epidemiology and pathophysiology

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 day-time lower urinary tract (LUT) conditions to group together all functional bladder problems in children.

Normal storage and emptying of the bladder at a socially accepted place and time is mostly achieved by age three to four. The 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 day-time symptoms is known as 'enuresis' and considered as a different entity (see chapter 3.10) [395].

As different studies have used varying definitions and criteria, it is difficult to give reliable percentages regarding the incidence of this problem. Reported prevalence ranges widely from 1% to 20% [396-404]. Due to increasing awareness and better access to specialised health care, the prevalence seems to be increasing [405, 406].

Lower urinary tract conditions in children may be due to disturbances of the filling phase, the voiding phase or a combination of both in varying severity. Mainly the conditions are divided into either overactive bladder (OAB) or dysfunctional voiding. They can, of course, coincide and one may even be causative of the other. Dysfunctional bowel emptying may also be part of the clinical problems and bladder bowel dysfunction (BBD) is the term used to cover concomitant bladder and bowel disturbances.

Lower urinary tract conditions are considered to be the result of incomplete or delayed maturation of the bladder sphincter complex. The pons is considered to be responsible for detrusor sphincter co-ordination

while the cortical area is responsible for inhibition of the micturition reflex and voluntary initiation of micturition. Therefore overactivity would be the result of delayed maturation of cortical control, while dysfunctional voiding would be the result of non-maturation of the co-ordination. Detrusor overactivity should not be considered as a sole bladder based problem but more a symptom of a centrally located dysfunction affecting bladder, bowel and even mood and behaviour [407].

A link between LUT and behavioural disorders such as ADHD (attention deficit/ hyperactivity disorder) has also been shown [408-411].

#### 3.9.1.1 *Filling-phase (storage) dysfunctions*

In filling-phase dysfunctions, the detrusor can be overactive, as in OAB, or underactive, as in underactive bladder (UAB). 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 of vesicoureteric reflux. Constipation can be an additional aetiological factor, which needs to be assessed. 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.

#### 3.9.1.2 *Voiding-phase (emptying) dysfunctions*

In voiding-phase (emptying), 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 pressures and PVRs. Symptoms will vary depending on the severity of inco-ordination between bladder and the sphincter. Staccato voiding is in less severe forms and interrupted voiding and straining is in more severe forms. Children with dysfunctional voiding are also prone to constipation and recurrent UTIs [412].

Incomplete emptying, 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 is been shown that LUTD is more significant for the occurrence of UTI than VUR itself [413]. 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.

#### 3.9.2 **Diagnostic evaluation**

The evaluation of LUT conditions includes medical and voiding history (bladder diaries and structured questionnaires), a physical examination, a urinalysis, and uroflowmetry with post void residual. The upper urinary tract needs to be evaluated in children with recurrent infections and dysfunctional voiding. Uroflowmetry can be combined with pelvic floor electromyography to demonstrate overactivity of the pelvic floor muscles during voiding. Urodynamic studies are usually reserved for patients with therapy resistant dysfunctional voiding and those not responding to treatment who are being considered for invasive treatment [411, 414-417].

In addition to a comprehensive medical history a detailed voiding diary provides documentation of voiding and defecation habits, frequency of micturition, voided volumes, night-time urine output, number and timing of incontinence episodes, and fluid intake. Voiding diary should at least be done for two days, although longer observation periods are preferred. A voiding diary provides information about storage function and incontinence frequency, while a pad test can help to quantify the urine loss. In the paediatric age group, where the history is taken from both the caregivers and child together, a structured approach is recommended using a questionnaire. Many signs and symptoms related to voiding and wetting will be unknown to the caregivers and should be specifically requested, using the questionnaire as a checklist. Some symptom scorings have been developed and validated [418, 419]. Although the reliability questionnaires are limited they are practical in a clinical setting to check the presence of the symptoms and have also been shown to be reliable to monitor the response to treatment. 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 [420, 421].

Urinalysis and urinary culture are essential to evaluate for UTI. Since transient voiding symptoms are common in the presence of UTI, exclusion of UTI is essential before further management of symptoms.

During clinical examination, genital inspection and observation of the lumbosacral spine and the lower extremities are necessary to exclude obvious uropathy and neuropathy.

Uroflowmetry with post-void residual evaluates the emptying ability, while an upper urinary tract US screens for (secondary) anatomical changes. 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 more uroflowmetry tests, which 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 [422, 423].

In the case of treatment failure re-evaluation is warranted and (video)-urodynamic (VUD) studies and neurological evaluation may be considered. Sometimes, there are minor, underlying, urological or neurological problems, which can only be suspected using VUD. In these cases, structured psychological interviews to assess social stress should be added [424] (LE: 1b).

Video-urodynamics may also be used as initial investigational tool in patients with suspicion of reflux. In this case reflux may be observed along with bladder dynamics. In the case of anatomical problems, such as posterior urethral valve problems, syringocoeles, congenital obstructive posterior urethral membrane (COPUM) or Moormann's ring, it may be necessary to perform cystoscopy with treatment. If neuropathic disease is suspected, MRI of the lumbosacral spine and medulla can help to exclude tethered cord, lipoma or other rare conditions.

### 3.9.3 **Management**

The treatment of LUTD involves a multimodal approach, involving strategies such as behavioural modification, and anticholinergic medication along with underlying and potentially complicating conditions such as constipation and UTIs.

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.

Strategies to achieve these goals include:

- 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 urinary infections 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 [405] as LUTS may disappear after successful management of bowel dysfunction.

Addition of other strategies, as below, may be needed:

- Pelvic floor muscle awareness practices with repeated sessions of biofeedback visualisation of uroflow curves and/or pelvic floor activity and relaxation,
- Clean intermittent self-catheterisation for large post-void residual volumes of urine

- Antimuscarinic drug therapy if detrusor overactivity is present.
- If the bladder neck is associated with increased resistance to voiding, alpha-blocker drugs may be introduced.

Treatment efficacy can be evaluated by improvement in bladder emptying and resolution of associated symptom. Controlled studies of the various interventions are needed. As with detrusor overactivity, the natural history of untreated dysfunctional voiding is not well delineated and optimum duration of therapy is poorly described. A high success rate has been described for urotherapy programmes, independent of the components of the programme. However, the evidence level is low as most studies of urotherapy programmes are retrospective and non-controlled [425].

### 3.9.3.1 *Specific interventions*

As well as urotherapy, there are some specific interventions, including physiotherapy (e.g. pelvic floor exercises), biofeedback, alarm therapy and neuromodulation. Although good results with these treatment modalities have been reported, the level of evidence remains low, since only a few RCTs were published [361, 426-431].

A systematic review reports that biofeedback is an effective, non-invasive method of treating dysfunctional voiding, and approximately 80% of children benefited from this treatment. However, most reports were of low level of evidence and studies of more solid design such as RCT should be conducted [432].

A more recently published multicentre controlled trial of cognitive treatment, placebo, oxybutynin, bladder and pelvic floor training did not report better results with oxybutynin and pelvic floor training compared to standard urotherapy [424](LE: 1b).

Two RCTs on underactive bladder without neurophatic disease have recently been published. Transcutaneous interferential electrical stimulation and animated biofeedback with pelvic floor exercise have been shown to be effective [433, 434]. In some cases, pharmacotherapy may be added. Some studies on orthosympathomimetics have been published with a low level of evidence [435].

Overactive bladder is common in the paediatric population. Although a stepwise approach starting with behavioural therapy is advised, antimuscarinic agents remain the mainstay of medical treatment for OAB. Oxybutynin is the most commonly used antimuscarinic in the paediatric population. The response to antimuscarinics varies and many experience serious side effects. Although there have been reports about the use of tolterodine, fesoterodine, trospium, propiverine, and solifenacin in children, to date, most of them are off label depending on age and national regulations. A few RCTs have been published, one on tolterodine showed safety but not efficacy [436], while another on propiverine showed both safety and efficacy [437] (LE: 1). The recent study on solifenacin showed its efficacy with side effects like constipation and electrocardiogram changes [438].

The difference in results is probably due to study design. Despite the low level of evidence for the use of anticholinergics and antimuscarinics, their use is recommended because of the large number of studies reporting a positive effect on OAB symptoms. Although  $\alpha$ -blocking agents are used occasionally, an RCT showed no benefit [439]. Botulinum toxin injection seems promising, but can only be used off-label [440].

A meta-analysis reports that neuromodulation therapy may lead to better partial improvement of non-neurogenic OAB; however, it may not render a definitive complete response. Office-based neuromodulation seems more efficacious than self-administered neuromodulation [441].

These new treatment modalities can only be recommended for standard therapy resistant cases [442]. Despite early successful treatment, there is evidence that there is a high recurrence rate of symptoms in the long-term which necessitates long term follow-up [443]. In addition, many patients may present themselves later in adulthood with different forms of LUTD [444].

### 3.9.4 **Summary of evidence and recommendations for the management of day-time lower urinary tract conditions**

Summary of evidence	LE
The term 'bladder bowel dysfunction' should be used rather than 'dysfunctional elimination syndrome and voiding dysfunction'.	4
Day-time LUTS has a high prevalence (1% to 20%).	2

Recommendations	LE	Strength rating
Use two day voiding diaries and/or structured questionnaires for objective evaluation of symptoms, voiding drinking habits and response to treatment.	2	Strong
Use a stepwise approach, starting with the least invasive treatment in managing day-time lower urinary tract dysfunction in children.	4	Weak
Initially offer urotherapy involving bladder rehabilitation and bowel management.	2	Weak
If bladder bowel dysfunction is present, treat bowel dysfunction first, before treating the lower urinary tract condition.	2	Weak
Use pharmacotherapy (mainly antispasmodics and anticholinergics) as second line therapy in overactive bladder.	1	Strong
Use antibiotic prophylaxis if there are recurrent infections.	2	Weak
Re-evaluate in case of treatment failure; this may consist of (video) urodynamics MRI of lumbosacral spine and other diagnostic modalities, guiding to off-label treatment which should only be offered in highly experienced centres.	3	Weak

## 3.10 **Monosymptomatic nocturnal enuresis - bedwetting**

### 3.10.1 **Epidemiology, aetiology and pathophysiology**

Monosymptomatic nocturnal enuresis, also known as bedwetting, is defined as an intermittent nocturnal incontinence. It is a relatively frequent symptom in children, 5-10% at seven years of age and 1 – 2% in adolescents. With a spontaneous yearly resolution rate of 15% (at any age), it is considered as a relatively benign condition [422, 445]. 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 nocturnal enuresis” is used when a child or adult begins wetting again after having stayed dry.

Non-monosymptomatic nocturnal enuresis is defined as the condition of nocturnal enuresis in association with day-time lower urinary tracts symptoms (LUTS, recurrent UTIs and/or bowel dysfunction) [445, 446].

Nocturnal enuresis has significant secondary stressful, emotional and social consequences for the child and their caregivers. Therefore treatment is advised from the age of six to seven years onwards considering mental status, family expectations, social issues and cultural background.

There is a clear hereditary factor in nocturnal enuresis. If none of the parents or their immediate relatives has suffered from bedwetting, the child has a 15% chance of wetting its 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 [446]. There is also a gender difference: 2 boys / 1 girl at any age.

The high arousal is the most important pathophysiological factor; the child does not wake up when the bladder is full. In addition to the high arousal, there needs to be an imbalance between night-time urine output and night-time bladder capacity and activity [422, 445, 446]. 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 [447] (LE: 1).

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. Symptoms such as habitual snoring, apnoeas, excessive sweating at night and mouth breathing in the patient history or via sleep questionnaires can lead to the diagnosis of adenotonsillar hypertrophy.

### 3.10.2 **Diagnostic evaluation**

The diagnosis is mainly obtained by history-taking. Focused questions to differentiate monosymptomatic vs.

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 voiding and drinking diary, which records day-time bladder function and drinking habits will further exclude comorbid factors such as LUTS and polydipsia.

The night-time urine production should be registered by weighing the night-time diapers in the morning and adding the first morning voided volume [448]. The night-time urine production should be recorded over an (at least) two week period to diagnose an eventual differentiation between a high night-time production (more than 130% the age expected bladder capacity) versus a night-time overactive bladder.

A physical examination should be performed with special attention to 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 urinary tract infections, or inexplicable polydipsia.

A uroflowmetry and ultrasound is indicated only if there is a history of previous urethral or bladder surgery, straining while voiding, interrupted voiding, an abnormal weak or strong stream, a prolonged voiding time.

If the comorbid factor of possible sleep disordered breathing occurs, a referral to an ear-nose-throat (ENT) specialist should be advised.

If the comorbid factor of developmental, attention or learning difficulties, family problems, parental distress and possible punishment of the child, a referral to a psychologist should be advised and followed-up.

### 3.10.3 **Management**

Before introducing any form of possible treatment, it is of utmost importance to explain the bedwetting condition to the child and the caregivers in order to demystify the problem.

#### 3.10.3.1 *Supportive treatment measures*

Initially, supportive measures including normal and regular eating and drinking habits should be reviewed, stressing normal fluid intake during the day and reducing fluid intake in the hours before sleep. Keeping a chart depicting wet and dry nights, also called as basic bladder advice, has not been shown to be successful in the early treatment for nocturnal enuresis [449] (LE:1a).

#### 3.10.3.2 *Conservative wait and see approach*

If the child and its family is 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. 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.

#### 3.10.3.3 *Nocturnal enuresis wetting alarm treatment*

The nocturnal alarm treatment is the use of a device that is activated by getting wet. The goal is that the child wakes up by the alarm, which can be acoustic or tactile, either by itself or with the help of a care giver. The method of action is to repeat the awakening and therefore change the high arousal to a low arousal, specifically when a status of full bladder is reached. It is of utmost importance that the child is collaborating. Initial success rates of 80% are realistic, with low relapse rates, especially when night-time diuresis does not exceed age expected bladder capacity. [450]. Regular follow-up will improve the success.

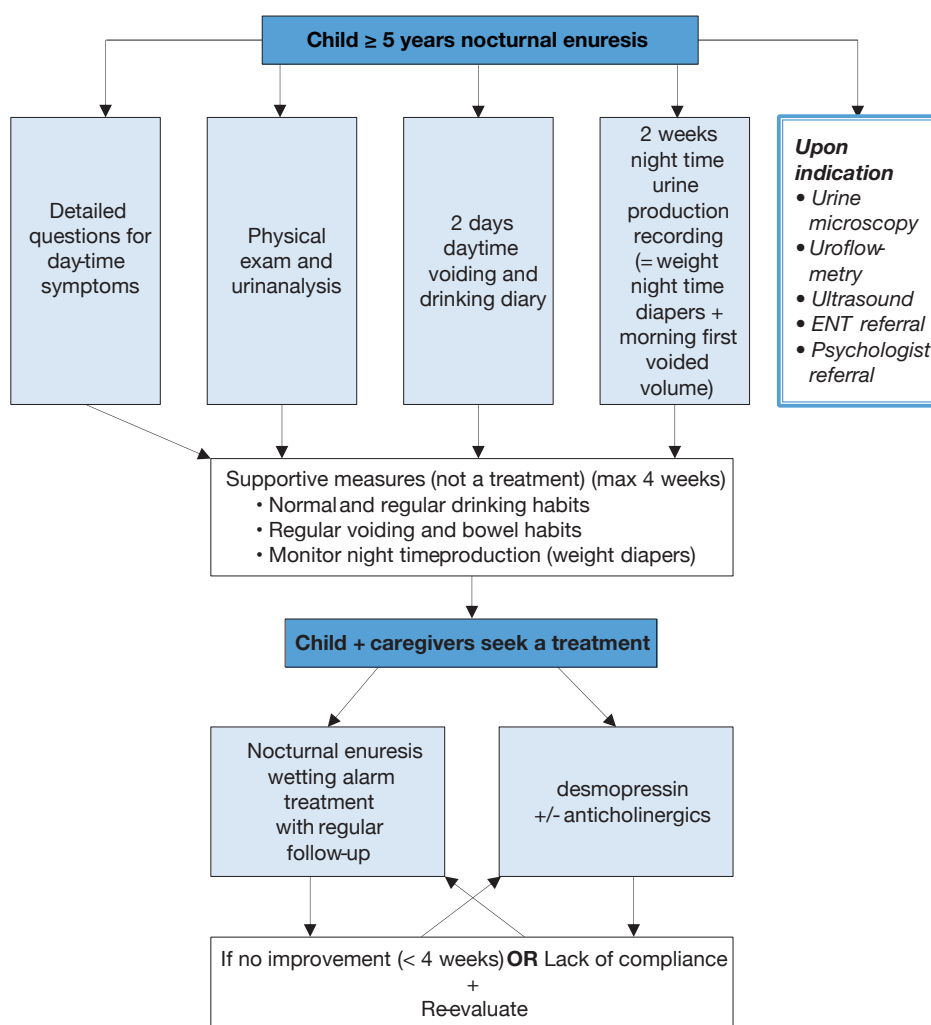
#### 3.10.3.4 *Medical therapy*

In the case of high night-time diuresis, success rates of 70% can be obtained with desmopressin (DDAVP), either as tablets (200-400µg), or as sublingual DDAVP oral lyophilisate (120-240 µg). A nasal spray is no longer recommended due to the increased risk of overdose [451, 452] (LE: 1). Relapse rates can be high after DDAVP discontinuation [448], however recently, structured withdrawal has shown lower relapse rates [453] (LE: 1).

In the event of desmopressin resistant treatment for nocturnal enuresis or if a suspicion exists for night-time OAB, combination with antispasmodics or anticholinergics is safe and efficient [448]. Imipramine, which has been popular for treatment of the enuresis, achieves only a moderate response rate of 50% and has a high relapse rate. Furthermore, cardiotoxicity and death from overdose are described, its use should therefore be discouraged as the first line therapy [454] (LE: 1). Figure 5 presents stepwise assessment and management options for nocturnal enuresis.

Although the several forms of neuromodulation and acupuncture have been investigated for nocturnal enuresis treatment, the present literature data precludes its use because of its inefficiency, or at least no additional benefit.

Figure 5 A stepwise assessment and management options for nocturnal enuresis



ENT = ear, nose and throat.

3.10.4 **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

Recommendations	LE	Strength rating
Do not treat children less than five years of age in whom spontaneous cure is likely, but 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.	2	Strong
Use voiding diaries or questionnaires to exclude day-time symptoms.	2	Strong
Perform a urine test to exclude the presence of infection or potential causes such as diabetes insipidus.	2	Strong
Offer supportive measures in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important.	1	Strong
Offer desmopressin in proven night-time polyuria.	1	Strong
Offer alarm treatment in motivated and compliant families.	1	Strong

### 3.11 Management of neurogenic bladder

#### 3.11.1 *Epidemiology, aetiology and pathophysiology*

Neurogenic detrusor-sphincter dysfunction (NDSF) can develop as a result of a lesion at any level in the nervous system. This condition contributes to various forms of LUTD, which may lead to incontinence, UTIs, VUR, and ultimately to renal scarring and renal failure requiring dialysis and/or transplantation. Conservative treatment starting in the first year of life is the first choice, however, surgery may be required at a later stage to establish adequate bladder storage, continence and drainage later on [455-457]. The main goals of treatment concerning the urinary tract are prevention of UTI's, urinary tract deterioration, achievement of continence at an appropriate age and promoting as good a QoL as possible. With regard to the associated bowel dysfunction, stool continence, with evacuation at a social acceptable moment, is another goal as well as education and treatment of disturbance in sexual function. Due to the increased risk of development of latex allergy, latex-free products (e.g., gloves, catheters etc.) should be used from the very beginning whenever possible [458].

Neurogenic bladder in children with myelodysplasia presents with various patterns of Detrusor-Sphincter-Dyssynergia (DSD) with a wide range of severity [459]. About 12% of neonates with myelodysplasia have no signs of neuro-urological dysfunction at birth [460]. Newborns with myelodysplasia and initially normal urodynamic studies are at risk for neurological deterioration secondary to spinal cord tethering, especially during the first six years of life. Close follow-up of these children is important for the early diagnosis and timely surgical correction of tethered spinal cord, and for the prevention of progressive urinary tract deterioration [460]. At birth, the majority of patients have normal upper urinary tracts (UUTs), but up to 60% develop upper tract deterioration due to bladder changes, UTI and /or VUR, if not treated properly [461-464]. Even today in a contemporary series around 50% of the patients are incontinent and 15% have an impaired renal function at the age of 29 years [465]. A recent systematic review concerning the outcome of adult meningomyelocele patients demonstrated that around 37% (8-85%) are continent, 25% have some degree of renal damage and 1.3% end stage renal failure [466]. The term "continence" is used differently in the reports, and the definition of "always dry" was used in only a quarter of the reports [467].

The most common presentation at birth is myelodysplasia. The incidence of neural tube defects in Europe is 9.1 per 10,000 births and has not decreased in recent years, despite longstanding recommendations concerning folic acid supplementations [468]. The term myelodysplasia includes a group of developmental anomalies that result from defects in neural tube closure. Lesions include spina bifida aperta and occulta, meningocele, lipomyelomeningocele, or myelomeningocele. Myelomeningocele is by far the most common defect seen and the most detrimental.

With antenatal screening spina bifida can be diagnosed before birth with the possibility of intrauterine closure of the defect [469, 470]. Traumatic and neoplastic spinal lesions of the cord are less frequent in children, but can also cause severe urological problems. Other congenital malformations or acquired diseases can cause a neurogenic bladder, such as total or partial sacral agenesis which can be part of the caudal regression syndrome [471]. In any child presenting with anorectal malformation (ARM) and cloacal malformations, the development of a neurogenic bladder is possible [472]. Patients with cerebral palsy may also present with varying degrees of voiding dysfunction, usually in the form of uninhibited bladder contractions (often due to spasticity of the pelvic floor and sphincter complex) and wetting. Finally, a "non-neurogenic neurogenic" bladder, such as Hinman or Ochoa syndrome, has been described, in which no neurogenic anomaly can be found, but severe bladder dysfunction as seen in neurogenic bladders is present [473, 474].

#### 3.11.2 *Classification systems*

As bladder sphincter dysfunction is poorly correlated with the type and spinal level of the neurological lesion, urodynamic and functional classifications are much more practical for defining LUT- pathology and planning treatment in children.

The bladder and sphincter are two units working in harmony to act as a single functional unit. In patients with a neurogenic disorder, the storage and emptying phase of the bladder function can be disturbed. The bladder and sphincter may function either overactive or underactive and present in 4 different combinations. This classification system is based on the urodynamic findings [475-477]:

- Overactive sphincter and overactive bladder
- Overactive sphincter and underactive bladder
- Underactive sphincter and overactive bladder
- Underactive sphincter and underactive bladder



### 3.11.3 **Diagnostic evaluation**

Today several guidelines and timetables are used [478-480]. The Panel advocate a proactive management in children with spinal dysraphism. In those with a safe bladder during the first urodynamic investigation, the next urodynamic investigation can be delayed until one year of age.

#### 3.11.3.1 *History and clinical evaluation*

History should include questions on CIC frequency, urine leakage, bladder capacity, UTI, medication, bowel function as well as changes of neurological status. A thorough clinical evaluation is mandatory including the external genitalia and the back. A two day diary, recording drinking volume and times as well as CIC intervals, bladder volume and leakage can provide additional information about the efficacy of the treatment.

#### 3.11.3.2 *Laboratory & Urinalysis*

After the first week of life, the plasma creatinine level should be obtained, later in life; the cystatin level is more accurate [481, 482]. If there is any sign of decreased renal function, physicians should be encouraged to optimise the treatment as much as possible.

The criteria for urine analysis are the same as for UTI (refer to Chapter 3.8). However, it is much easier for caregivers or patients to obtain a catheter urine in patients, who are on CIC. They can also perform a dip stick analysis to screen for UTI at home. For relevance see 3.11.4.5.

#### 3.11.3.3 *Ultrasound*

At birth, ultrasound of the kidneys and bladder should be performed and then repeated at least annually. If there are any clinical changes in between, another ultrasound should be performed. Dilatation of the UUT should be reported according to the classification system of Society of Foetal Urology [483] including the measurement of the caliceal dilatation and anterior posterior diameter of the renal pelvis. Residual urine and bladder wall thickness should also be mentioned. A dilated ureter behind the bladder should be recorded. Bladder wall thickness has been shown not to be predictive of high pressures in the bladder during voiding and storage and cannot be used as a non-invasive tool to judge the risk for the upper urinary tract [484].

#### 3.11.3.4 *Urodynamic studies/videourodynamic*

Urodynamic studies (UD) are one of the most important diagnostic tools in patients with neurogenic bladders. In newborns with spina bifida aperta (failure of mesodermal in-growth over the developing spinal canal results in an open lesion most commonly seen in the lumbosacral area including an incomplete closure of the vertebral column and not covered by skin), the first UD should be performed after the phase of the spinal shock after closure, usually between the second and third months of life [485]. Especially in newborns, performing and interpretation of urodynamic studies may be difficult, as no normal values exist. After that it should be repeated annually, depending on the clinical situation. During and after puberty bladder capacity, maximum detrusor pressure and detrusor leak point pressure increase significantly [486]. Therefore, during this time, a careful follow-up is mandatory.

##### 3.11.3.4.1 Preparation before urodynamic studies

Before any UD a urine analysis should be done. The first assessment should be done under antibiotic prophylaxis. A Cochrane analysis of nine randomised controlled trials showed, that the administration of prophylactic antibiotics compared to placebo reduced the risk of significant bacteriuria from 12% to 4% after UD-studies. However, this was without significant difference for symptomatic UTI (20% versus 28%), fever or dysuria [487]. If there is a significant bacteriuria, antibacterial treatment should be discussed; especially in older patients a single shot may be sufficient [488].

Generally UD-parameters should include:

- the bladder cystometric capacity;
- the intravesical filling pressure;
- detrusor compliance;
- the intravesical pressure at the moment of voiding or leakage;
- the presence or absence of overactive detrusor;
- the competence of the internal and external sphincter;
- the degree of synergy of the detrusor and sphincter during voiding;
- the post-voiding residual urine volume.

In the infant period information on detrusor filling pressure and the pressure and bladder volume at which the child voids or leaks can be obtained [485]. Detrusor leak point pressure is more accurate than abdominal leak point pressure, but keeping the rectal probe in an infant in place can be challenging [485]. Addition of

fluoroscopy (video-urodynamic study) will provide information about presence of VUR, at what pressures VUR starts and the configuration of the bladder neck during filling and leakage or voiding.

#### 3.11.3.4.2 Uroflowmetry

Unlike in children with non-neurogenic voiding dysfunction, uroflowmetry can rarely be used since most affected patients do not void spontaneously. In those with cerebral palsy, non-neurogenic-neurogenic bladder or other neurological conditions allowing active voiding it may be a practical tool. It provides an objective way of assessing the efficiency of voiding, while recording of pelvic floor activity with electromyography (EMG) can be used to evaluate synergy between detrusor and the sphincter. The post void residual urine is measured by US. The main limitation of uroflowmetry is a compliant child to follow instructions [489-492].

#### 3.11.3.5 Urodynamic studies

The standards of the ICCS should be applied to the UD in patients with neurogenic bladders and accordingly reported [475, 493]. Natural fill UD in children with neurogenic bladder detects more overactivity compared with diagnoses delivered by conventional UD [494, 495]. It may be an option in patients where the findings in the normal UD are inconsistent with clinical symptoms and other clinical findings [495].

#### 3.11.3.6 Voiding cystourethrogram

If video-urodynamic equipment is not available, a VCUG with UD is an alternative to confirm or exclude VUR and visualise the lower urinary tract including the urethra.

#### 3.11.3.7 Renal scan

DMSA (Technetium Dimercapto-Succinic Acid) Renal scan is the gold standard to evaluate renal parenchyma. In contemporary series, renal scars can be detected in up to 46% as patients get older [496-498]. A positive DMSA-Scan correlates well with hypertension in adulthood, whereas ultrasound has a poor correlation with renal scars [498]. Therefore, a DMSA scan as a baseline evaluation in the first year of life is recommended.

### 3.11.4 Management

The medical care of children with neurogenic bladder requires an on-going multidisciplinary approach. There is some controversy about optimal timing of the management; proactive vs. expectant management [455-457]. Even with a close expectant management e.g. in one series 11/60 need augmentation within a follow-up of 16 years and 7/58 had a decrease in total renal function, which was severe in 2 [499]. During the treatment it should be also taken into account with spina bifida patients, that QoL is related to urinary incontinence independent from the type and level of spinal dysraphism and the presence or absence of a liquor shunt [500].

Foetal open and endoscopic surgery for meningocele are performed to close the defect as early as possible to reduce the neurological, orthopaedic and urological problems [501]. In the MOMS-Trail, Brooks *et al* found no difference between those closed *in utero* vs. those closed after birth concerning the need for CIC [470], but less trabeculation in the prenatal surgery group. Mean gestation age (28.3 vs. 35.2) seems to have no initial impact on bladder function in the first few years of life [502]. Despite some promising reports [502-505], caregivers need to be aware about the high risk of developing a neurogenic bladder as demonstrated by the Brazilian group [506]. Regular and close follow-up examinations including UD are indicated in all these patients.

#### 3.11.4.1 Early management with intermittent catheterisation

Starting intermittent catheterisation soon after birth and closure of the defect by the neurosurgeon in all infants has shown to decrease renal complications and the need for later augmentation [507-509]. In infants without any clear sign of outlet obstruction, this may be delayed but only in very selected cases. These infants should be monitored very closely for UTIs and changes of the urinary tract with US and UD. The early initiation of IC in the newborn period makes it easier for caregivers to master the procedure and for children to accept it, as they grow older [510, 511].

A Cochrane review as well as some recent studies showed, that there is a lack of evidence to state that the incidence of UTI is affected by use of sterile or clean technique, coated or uncoated catheters, single (sterile) or multiple use (clean) catheters, self-catheterisation or catheterisation by others, or by any other strategy [512-515]. Looking at the microbiological milieu of the catheter, there was a trend for reduced recovery of potentially pathogenic bacteria with the use of hydrophilic catheters. Also, a trend for a higher patient satisfaction with the use of hydrophilic catheters was seen [516]. Based on the current data, it is not possible to state that one catheter type, technique or strategy is better than another.

#### 3.11.4.2 Medical therapy

Antimuscarinic/anticholinergic medication reduces/prevents detrusor overactivity and lowers the intravesical

pressure [517, 518]. Effects and side effects depend on the distribution of the M1-M5 receptors [519]. In the bladder, the subtype M2 and M3 are present [518, 520]. Oxybutynin is the most frequently used in children with neurogenic bladder with a success rate of up to 93% [521, 522]. Dose dependent side-effects (such as dry mouth, facial flushing, blurred vision heat intolerance etc.) limit the use. Intravesical administration has a significant higher bioavailability due to the circumvention of the intestinal first pass metabolism, as well as possible local influence on C-fiber-related activity can be responsible for the different clinical effect [523, 524]. Intravesical administration should be considered in patients with severe side-effects, as long-term results demonstrated that it was well tolerated and effective [525, 526]. The transdermal administration leads also to a substantial lower ratio of N-desethoxybutynin to oxybutynin plasma levels, however, there are treatment related skin reactions in 12/41 patients [527]. There are some concerns about central anticholinergic adverse effects associated with oxybutynin [528, 529]. A double blinded cross-over trial, as well as a case control study, showed no deleterious effect on children's attention and memory [530, 531]. Tolterodine, solifenacin, trospium chloride and propiverine and their combinations can be also used in children [532-538]. The oral dosage for oxybutynin is up to 0.2mg/kg/every 8 hours [518] given three times daily. The intravesical dosage can be up to 0.7 mg/kg/daily and transdermal 1.3-3.9 mg/daily. The dosage of the other drugs is: Tolterodine 0.5 – 4 mg/day divided in two doses, Solifenacin 1.25 up to 10 mg per day (single dose), Propiverin 0.8mg/kg/day divided in two dosages and trospium chloride up to 3 times 15 mg starting with 3 times 5 mg. Except for oxybutynin, all other anticholinergic drugs are off label use, which should be explained to the caregivers.

Early prophylactic treatment with anticholinergics showed a lower rate of renal deterioration as well as a lower rate of progression to bladder augmentation [507, 509, 539].

$\beta_3$  agonists like mirabegron may be also an alternative agent and may be effective in patients with neurogenic bladders. Up to date, there is almost no experience with this drug [540], therefore no recommendation can be made.

$\alpha$ -adrenergic antagonists may facilitate emptying in children with neurogenic bladder [541]. Doxazosin with an initial dose of 0.5 to 1.0 mg or tamsulosin hydrochloride in a medium (0.0002-0.0004mg/kg/day) or high dose (0.0004-0.0008 mg/kg/day) has been given to children with neurogenic bladders [541-543]. It was well tolerated but not effective at least in one study [542].

Botulinum toxin A injections: In neurogenic bladders that are refractory to anticholinergics, the off-label use of suburothelial or intramuscular injection of onabotulinum toxin A into the detrusor muscle is a treatment option [544, 545]. In children, continence could be achieved in 32-100% of patients, a decrease in maximum detrusor pressure of 32% to 54%, an increase of maximum cystometric capacity from 27% to 162%, and an improvement in bladder compliance of 28%-176% [544]. Onabotulinum toxin A seems to be more effective in bladders with obvious detrusor muscle over-activity, whereas non-compliant bladders without obvious contractions are unlikely to respond [546, 547]. Also, the injections into the trigone seems to be save in regard of reflux and upper tract damage, if it has some benefit is not further investigated [548].

The most commonly used dose of onabotulinum toxin A is 10 to 12 U/kg with a maximum dose between 200 U and 360 U [544]. However, in one study, 5U/kg were used with comparable results [549]. Up to date, no randomised dose titration study has been published in children. The optimal dose in children as well as the time point when to inject which child is still unclear. Onabotulinum toxin A can be effective between three to twelve (0-25) months and repeated injections are effective up to ten years in one study [545, 550, 551].

Urethral sphincter onabotulinum toxin A injection has been shown to be effective in decreasing urethral resistance and improve voiding. The evidence is still too low to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases [552, 553].

#### Neuromodulation

Intravesical electrical stimulation of the bladder [554-556], sacral nerve stimulation [557, 558] and transcutaneous neuromodulation [559] are still experimental and cannot be recommended outside from clinical trials. The same is true for the intradural somatic-to-autonomic nerve anastomosis [560, 561].

#### Urethral Dilatation

The aim is to lower the pop-off pressure by lowering the detrusor leak-point pressure by dilatation of the external sphincter under general anaesthesia up to 36 Charr. Some studies showed, that especially in females, the procedure is safe and in selected patients, effective [562-564].

#### Vesicostomy

Vesicostomy - preferably a Blocksom stoma [565] - is an option to reduce bladder pressure in children/newborns, if the caregivers are incontinent with IC and/or IC through the urethra is extremely difficult or impossible [566-568]. Especially in the young infant with severe upper tract dilatation or infections, a vesicostomy should be considered. Drawbacks are the problem to fit and maintain a collecting appliance in

older patients. A cystostomy button may be an alternative, with a complication rate (mostly UTI) of up to 34% within a mean follow-up of 37 months [569].

#### 3.11.4.3 *Management of faecal incontinence*

Children with neurogenic bladder usually have also a neurogenic bowel function. Faecal incontinence may have an even greater impact on QoL, as the odor can be a reason for social isolation. The aim of each treatment is to obtain a smooth, regular bowel emptying and to achieve continence and impotence. The regime should be tailored to the patient's need, which may change over time. Beside a diet with small portioned fibre food and adequate fluid intake to keep a good fluid balance [518], follow-up options should be offered to the patients and caregivers.

At the beginning, faecal incontinence is managed most commonly with mild laxatives, such as mineral oil, combined with enemas to facilitate removal of bowel contents. To enable the child to defecate once a day at a given time rectal suppositories as well as digital stimulation by parents or caregivers can be used. Today, transanal irrigation is one of the most important treatments for patients with neurogenic bowel incontinence. Regular irrigations significantly reduce the risk for faecal incontinence and may have a positive effect on the sphincter tonus as well as the rectal volume [570]. The risk of irrigation induced perforation of the bowel is estimated as one per 50,000 [571]. During childhood, most children depend on the help of the caregivers. Later in some of them, transanal irrigation becomes difficult or impossible due to anatomic or social circumstances. In these patients antegrade irrigation using a MACE-stoma (Malone Antegrade Continence Enema) is an option, which can also be placed in the left abdomen [572, 573]. In a long-term study of 105 patients, 69% had successful bowel management. They were started on normal saline, but were switched to GoLYTELY (PEG-3350 and electrolyte solution). Additives (biscodyl, glycerin etc.) were needed in 34% of patients. Stomal complications occurred in 63% (infection, leakage, and stenosis) of patients, 33% required surgical revision and 6% eventually required diverting ostomies [574]. In addition, patients need to be informed, that the antegrade irrigation is also time consuming with at least 20 – 60 minutes.

#### 3.11.4.4 *Urinary tract infection*

Urinary tract infections are common in children with neurogenic bladders. However, there is no consensus in most European centres, for prevention, diagnosing and treating UTIs in children with neurogenic bladders performing CIC [575]. Although bacteriuria is seen in more than half of children on CIC, patients who are asymptomatic do not need treatment [576-578]. Continuous antibiotic prophylaxis (CAP) creates more bacterial resistance as demonstrated by a randomised study. Those on stopping the prophylaxis had reduced bacterial resistance, however, 38/88 started antibiotic prophylaxis again due to recurrent UTIs or the caregivers request [579]. A cohort study with 20 patients confirmed these findings. Continuous antibiotic prophylaxis was not protective against the development of symptomatic UTIs and new renal scarring, however, increased the risk of bacterial resistance [580]. A randomised study in 20 children showed that cranberry capsules significantly reduced the UTI-rate as well as the rate of bacteriuria [581]. If VUR is present, prophylactic antibiotics should be started when patients experience recurrent UTIs [582, 583].

##### 3.11.4.4.1 *Urinary tract infection and clean intermittent catheterisation*

The incidence of asymptomatic bacteriuria ranges between 42% – 76% [510, 518, 584]. A cross-over study in 40 children with neurogenic bladder demonstrated, that the reuse of CIC-catheters for up to three weeks compared to one week increased the prevalence of bacteriuria from 34% to 74% (it was 60% at the start of the study). During the study-period of eighteen weeks, none of the patient developed a febrile UTI [585]. There is no medical benefit in performing CAP in children with neurogenic bladder, who perform CIC [518]. In those with recurrent UTI, intravesical instillation of gentamycin may be an option [586, 587].

#### Reflux

Secondary reflux in patients with neurogenic bladder increases the risk for pyelonephritis. The treatment is primary related to bladder function including anticholinergic therapy, CIC and may be later augmentation [588]. Those with early and post-therapy persistent reflux during videourodynamic studies at low pressure have a higher risk of pyelonephritis [589]. Patients with a high-grade reflux before augmentation have a higher risk for persistent symptomatic reflux after the enterocystoplasty [590]. Therefore simultaneous ureteral re-implantation in high grade symptomatic reflux especially in those with low-pressure high grade reflux should be discussed with the patient/caregivers. Endoscopic treatment has a failure rate of up to 75% after a median follow-up of 4.5 years [591] which is in contrast to the open techniques with a higher success rate [592], but may have an increased risk of inducing obstruction.

#### 3.11.4.5 *Sexuality*

Sexuality, while not an issue in childhood, becomes progressively more important as the patient gets older.

This issue has historically been overlooked in individuals with myelodysplasia. However, patients with myelodysplasia do have sexual encounters [593]. The prevalence of precocious puberty is higher in girls with meningomyelocele [594]. Studies indicate that at least 15-20% of males are capable of fathering children and 70% of females can conceive and carry a pregnancy to term. It is therefore important to counsel patients about sexual development in early adolescence.

Women seem to be more sexually active than men in some studies from the USA and the Netherlands [593, 595]; in an Italian study men were more active [596]. The level of the lesion was the main predictor to be sexually active [596, 597]. Erectile function can be improved by sildenafil in up to 80% of the male patients [598, 599]. Neurosurgical anastomosis between the inguinal nerve and the dorsal penile nerve in patients with a lesion below L3 and disturbed sensation is still to be considered as an experimental treatment [595, 600]. Only 17% to 1/3 of the patients talk to their doctors about sexuality, 25 – 68% were informed by their doctors about reproductive function [593]. Therefore, early discussion about sexuality in the adolescent is recommended and should be promoted by the paediatric urologist taking care of these patients.

#### 3.11.4.6 Bladder augmentation

In patients where conservative treatment including onabotulinum toxin A (for indication see 3.11.4.3) fails to keep a low-pressure reservoir with a good capacity and compliance, bladder augmentation should be offered. For augmentation, ileal and colonic segments can be used [601]. Gastric segments are rarely used due to its associated complications like the haematuria-dysuria syndrome as well as secondary malignancies, which arise earlier than with other intestinal segments [602-605]. Enterocystoplasty increases bladder capacity, reduces storage pressure and can improve UUT drainage [606]. Good socially acceptable continence rate can be achieved with or without additional bladder outlet procedures [607]. In those, who are not able to perform CIC through the urethra, a continent cutaneous channel should be offered. Surgical complications and revision rate in this group of patients is high. The 30-day all over event rate in the American College of Surgeons' National Surgical Quality Database is approximately 30% (23-33%) with a re-operation rate in this short time period of 13% [608, 609]. In these patients with long-life expectancy the complication rate clearly increases with the follow-up period [608-611]. The ten-year cumulative complication incidence from the Paediatric Health Information System showed a rate of bladder rupture in up to 6.4%, small bowel obstruction in up to 10.3%, bladder stones in 36%, pyelonephritis in more than a third of the patients and a re-augmentation rate of up to 13% [612]. Bladder perforation, as one of the worst complications, occurs in 6-13% [613]. The rate of VP-shunt infections after gastrointestinal and urological procedures ranges between 0-22%. In a recent study, bowel preparation seems not to have a significant influence on the infection rate (10.5 vs 8.3%) [614]. Not only surgical complications must be considered; also metabolic complications and consequences after incorporating bowel segments have to be taken into account, such as imbalance of the acid base balance, decrease vitamin B12 levels and loss of bone density. Stool frequency can increase as well as diarrhoea after exclusion of bowel segments [615] and last, but not least, these patients have a lifelong increased risk to develop secondary malignancies [616-618]. Therefore, a lifelong follow-up of these patients is required including physical examination, US, blood gas analysis, (pH and base excess), renal function and vitamin B12 if Ileum is used. Endoscopic evaluation starting ten years after augmentation is not cost-effective [619, 620], but may prevent some advanced cancer. Woodhouse *et al* do not recommend cystoscopy within the first fifteen years after surgery [621]. The real value of annual cystoscopic evaluation has not been proven by any study. Urodynamic studies after bladder augmentation are only indicated, if upper tract dilatation and/or incontinence after the operation has not improved [622].

Adverse effects of intestinal cystoplasties can be avoided by the use of ureterocystoplasty. The combination of a small contracted bladder, associated with a severe dilation of the ureter of a non-functioning kidney is quite rare. The technique was first described in 1973 by Eckstein [623]; the success rate depends on patient selection and the re-augmentation rate can reach 73% [624, 625].

Auto-augmentation with partial detrusorectomy or detrusor myotomy creating a diverticulum avoids metabolic complications with the use of intestinal segments. The reports are conflicting, therefore, it may be used in very selected cases [626-629]. For a successful outcome, a pre-operative bladder capacity of 75-80% of the expected volume seems necessary [630, 631]. Seromuscular cystoplasty has also not proven to be as successful as standard augmentation with intestine [632]. Tissue engineering, even if successful *in vitro* and some animal models, does not reach the results by using intestinal segments with a higher complication rate [633, 634]. Therefore, these alternatives for bladder augmentation should be considered as experimental and should be used only in controlled trials.

#### 3.11.4.7 Bladder outlet procedures

So far, no available medical treatment has been validated to increase bladder outlet resistance.  $\alpha$ -adrenergic receptor stimulation of the bladder neck has not been very effective [635-640]. Using fascial slings with

autologous fascial strip or artificial material a continence rate between 40 – 100% can be achieved. In most cases this is achieved in combination with bladder augmentation [641, 642]. Catheterising through a reconstructed bladder neck or a urethra compressed by a sling may not be easy; many surgeons prefer to combine this approach with a catheterisable channel [455]. In contrast to the autologous slings, artificial slings in girls with CIC through the urethra have a high complication rate [643]. In males, it may be an option [644], however as long as long-term results are missing this method has to be classified as experimental and should only be carried out in studies. Artificial urinary sphincters were introduced by Scott in 1973 [645]. The continence rates in the literature in selected patients can be up to 85% [646-649]. Postpubertal patients, who can void voluntarily are good candidates, if they are manually dexterous. In very selected patients, CIC through the sphincter in an augmented bladder is possible [650]. The erosion rate can be up to 29% and the revision-rate up to 100% depending on the follow-up time [651].

Patients, who underwent a bladder neck procedure only, have a chance of > 30% for an augmentation later on, half of them developed new upper tract damage in that time [652, 653]. In patients with a good bladder capacity and bladder compliance without an indication for bladder augmentation, there is a risk of postoperative changes of the bladder function. Therefore, a very close follow-up of these patients with UD is required to avoid upper tract damage and chronic renal failure.

Bladder neck reconstruction is used mostly in exstrophy patients with acceptable results. However, in children with a neurogenic bladder the results are less favorable [654]. In most patients, the creation of a continent catheterisable stoma is necessary due to difficulties to perform the CIC via urethra. In one series, 10% to a third still perform a CIC via urethra with a re-operation rate between 67% and 79% after a median follow-up between seven and ten years [655]. In patients who are still incontinent after a bladder outlet procedure, bladder neck closure with a continent catheterisable stoma is an option. The combination of a sling procedure together with a urethral lengthening procedure may improve the continence rates [656].

Bulking agents have a low success rate (10-40%), which is in most cases only temporary [657-659]. However, it does not adversely affect the outcome of further definite surgical procedures [660].

Bladder neck closure is often seen as the last resort to gain urinary continence in those patients with persistent urinary incontinence through the urethra. In girls, the transection is done between bladder neck and urethra and in boys above the prostate with preservation of the neurovascular bundle. It is an effective method to achieve continence together with a catheterisable cutaneous channel +/- augmentation as a primary or secondary procedure [661, 662]. A complication rate of up to 1/3 and a vesicourethral /vesicovaginal fistula in up to 15% should be considered [663], together with a higher risk for bladder stones, bladder perforation and deterioration of the upper tract function, if the patient is not compliant with CIC and bladder irrigations [663, 664].

#### 3.11.4.8 *Catheterisable cutaneous channel.*

In most patients with a neurogenic bladder IC is required. If this is not possible, or very time and/or resources consuming via the urethra, a continent cutaneous catheterisable channel should be offered as well as in those with bladder outlet procedures. It is especially beneficial to wheelchair-bound patients who often have difficulty with urethral catheterisation or are dependent on others to catheterise the bladder. In long-term studies the revision rate due to stenosis or incontinence can be as high as 50 to 60% depending on the type of channel [665, 666].

The stoma can be placed at the umbilicus or in the lower right abdominal wall using a VQZ plasty [667]. It should be carefully evaluated pre-operatively: it is extremely important that the patient can reach the stoma easily. Sometimes it has to be placed in the upper abdominal wall due to severe scoliosis mostly associated with obesity.

#### 3.11.4.9 *Continent and incontinent cutaneous urinary diversion*

Incontinent urinary diversion should be considered in patients, who are not willing or able to perform a CIC and who need urinary diversion because of upper tract deterioration or gain urinary continence due to social reasons. In children and adolescents, the colonic conduit has shown to have less complications compared to the ileal conduit [668-671]. Total bladder replacement is extremely rare in children and adolescents, but may be necessary in some adults due to secondary malignancies or complications with urinary diversions. Any type of major bladder and bladder outlet construction should be performed in centres with sufficient experience in the surgical technique, and with experienced healthcare personnel to carry out post-operative follow-up [607, 672, 673].

A simple algorithm can be used for management of these patients (Figure 6).

### 3.11.5 **Follow-up**

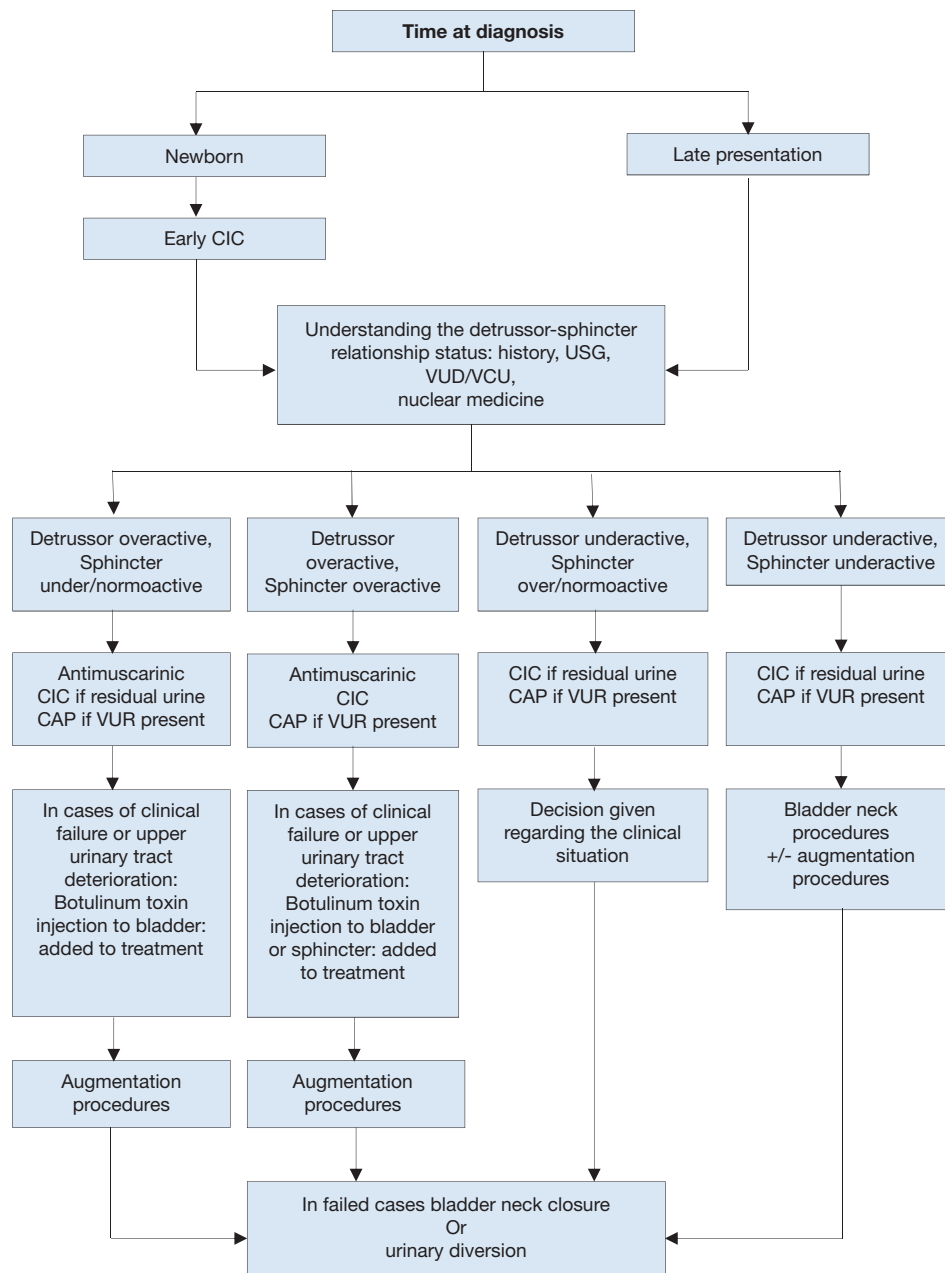
Neurogenic bladder patients require lifelong follow-up including not only urological aspects but also neurological and orthopaedic aspects. Regular investigation of upper and lower urinary tract is mandatory. In patients with changes of the function of the upper and/or lower urinary tract, a complete neurological re-investigation should be recommended including a total spine MRI to exclude a secondary tethered cord or worsening of the hydrocephalus. In addition, if some neurological changes are observed a complete investigation of the urinary tract should be undertaken.

In those patients with urinary tract reconstruction using bowel segments, regulatory investigations concerning renal function, acid base balance and vitamin B12 status are mandatory to avoid metabolic complications. There is an increased risk for secondary malignancies in patients with a neurogenic bladder either with or even without enteric bladder augmentations [617, 618, 674-680]. Therefore, patients need to be informed about this risk and possible signs like haematuria. Although there are poor data on follow-up schemes to discover secondary malignancies, after a reasonable follow-up time (e.g. ten to fifteen years), an annual cystoscopy can be considered.

### 3.11.6 **Self-organisation of patients**

As patients' self-organisations can support the parents, caregivers and the patients in all aspects of their daily life, patients should be encouraged to join these organisations.

Figure 6: Algorithm for the management of children with myelodysplasia with a neurogenic bladder



CAP = continuous antibiotic prophylaxis; CIC = clean intermittent catheterisation; US = ultrasound; VCUG = voiding cystourethrography; VUD = videourodynamic; VUR = vesicoureteric reflux.



### 3.11.7 Summary of evidence and recommendations for the management of neurogenic bladder

Summary of evidence	LE
Neurogenic detrusor-sphincter dysfunction may result in different forms of LUTD and ultimately result in incontinence, UTIs, VUR, and renal scarring.	2a
In children, the most common cause of NDSD is myelodysplasia (a group of developmental anomalies that result from defects in neural tube closure).	2
Bladder sphincter dysfunction correlates poorly with the type and level of the spinal cord lesion. Therefore, urodynamic and functional classifications are more practical in defining the extent of the pathology and in guiding treatment planning.	2a
Children with neurogenic bladder can have disturbances of bowel function as well as urinary function which require monitoring and, if needed, management.	2a
The main goals of treatment are prevention of urinary tract deterioration and achievement of continence at an appropriate age.	2a
Injection of botulinum toxin into the detrusor muscle in children who are refractory to anticholinergics, has been shown to have beneficial effects on clinical and urodynamic variables.	2a

Recommendations	LE	Strength rating
Urodynamic studies should be performed in every patient with spina bifida as well as in every child with high suspicion of a neurogenic bladder to estimate the risk for the upper urinary tract and to evaluate the function of the detrusor and the sphincter.	2	Strong
In all newborns, intermittent catheterisation (IC) should be started soon after birth. In those with a clear underactive sphincter and no overactivity starting IC may be delayed. If IC is delayed, closely monitor babies for urinary tract infections, upper tract changes (US) and lower tract (UD).	3	Strong
Start early anticholinergic medication in the newborns with suspicion of an overactive detrusor.	2	Strong
The use of suburothelial or intradetrusor injection of onabotulinum toxin A is an alternative and a less invasive option in children who are refractory to anticholinergics in contrast to bladder augmentation.	2	Strong
Treatment of faecal incontinence is important to gain continence and independence. Treatment should be started with mild laxatives, rectal suppositories as well as digital. If not sufficient transanal irrigation is recommended, if not practicable or feasible, a Malone antegrade colonic enema (MACE)/Antegrade continence enema (ACE) stoma should be discussed.	3	Strong
Ileal or colonic bladder augmentation is recommended in patients with therapy-resistant overactivity of the detrusor, small capacity and poor compliance, which may cause upper tract damage and incontinence. The risk of surgical and non-surgical complications and consequences outweigh the risk for permanent damage of the upper urinary tract +/- incontinence due to the detrusor.	2	Strong
In patients with a neurogenic bladder and a weak sphincter, a bladder outlet procedure should be offered. It should be done in most patients together with a bladder augmentation.	3	Weak
Creation of a continent cutaneous catheterisable channel should be offered to patients who have difficulties in performing an IC through the urethra.	3	Weak
A life long follow-up of renal and reservoir function should be available and offered to every patient. Addressing sexuality and fertility starting before/during puberty should be offered.	3	Weak
Urinary tract infections are common in children with neurogenic bladders, however, only symptomatic UTIs should be treated.	3	Weak

### 3.12 Dilatation of the upper urinary tract (UPJ and UVJ obstruction)

#### 3.12.1 *Epidemiology, aetiology and pathophysiology*

Dilatation of the UUT remains a significant clinical challenge in deciding which patient will benefit from treatment. Ureteropelvic junction (UPJ) obstruction is defined as impaired urine flow from the pelvis into the proximal ureter with subsequent dilatation of the collecting system and the potential to damage the kidney. It is the most common pathological cause of neonatal hydronephrosis [681]. It has an overall incidence of 1:1,500 and a ratio of males to females of 2:1 in newborns.

Ureterovesical junction (UVJ) obstruction is an obstructive condition of the distal ureter as it enters the bladder, commonly called a primary obstructive megaureter. Megaureters are the second most likely cause of neonatal hydronephrosis. They occur more often in males and are more likely to occur on the left side [682].

It can be very difficult to define 'obstruction' 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 [683].

#### 3.12.2 *Diagnostic evaluation*

The widespread use of US during pregnancy has resulted in a higher detection rate for antenatal hydronephrosis [684]. The challenge in the management of dilated UUT is to decide which child should be observed, which child should be managed medically, and which child 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 7).

##### 3.12.2.1 *Antenatal ultrasound*

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

- laterality, severity of dilatation, and echogenicity of the kidneys;
- hydronephrosis or hydro-ureteronephrosis;
- bladder volume and bladder emptying;
- sex of the child;
- amniotic fluid volume [685].

##### 3.12.2.2 *Postnatal ultrasound*

Since transitory neonatal dehydration lasts about 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 [686]. Ultrasound 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.

##### 3.12.2.3 *Voiding cystourethrogram*

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

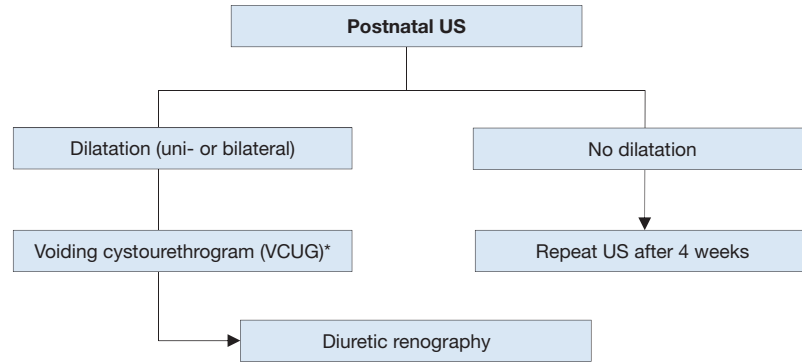
- vesicoureteral reflux (found in up to 25% of affected children) [687];
- urethral valves;
- ureteroceles;
- diverticula;
- neurogenic bladder.

Conventional VCUG is the method of choice for primary diagnostic procedures [688].

##### 3.12.2.4 *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 (99mTc) mercaptoacetyl triglycine (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 [689]. 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 15 mL/kg over 30 minutes, with a subsequent maintenance rate of 4 mL/kg/h throughout the entire time of the investigation [690]. The recommended dose of furosemide is 1 mg/kg for infants during the first year of life, while 0.5 mg/kg should be given to children aged one to sixteen years, up to a maximum dose of 40 mg.

**Figure 7: Diagnostic algorithm for dilatation of the upper urinary tract**



\* A diagnostic work-up including VCUG must be discussed with the caregivers, as it is possible that, even if reflux is detected, it may have absolutely no clinical impact. However, it should be borne in mind that reflux has been detected in up to 25% of cases of prenatally detected and postnatally confirmed hydronephrosis [687].  
US = ultrasound.

### 3.12.3 Management

#### 3.12.3.1 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, as it may still be capable of meaningful renal function, unlike a severely hypoplastic and dysplastic kidney.

It is important to be able to tell the caregivers exactly when they will have a definitive diagnosis for their child and what this diagnosis will mean. In some cases, however, it will be immediately obvious that the child is severely affected; there will be evidence of massive bilateral dilatation, bilateral hypoplastic dysplasia, progressive bilateral dilatation with oligohydramnios, and pulmonary hypoplasia.

Intrauterine intervention is rarely indicated and should only be performed in well-experienced centres [691].

##### 3.12.3.1.1 Antibiotic prophylaxis for antenatal hydronephrosis

The benefits and harms of continuous antibiotic prophylaxis (CAP) vs. observation in patients with antenatal hydronephrosis are controversial. Currently, only two RCTs have been published, one of which is a pilot trial [692] and the other publication is only available as a congress abstract [693]. Both publications present incomplete data and outcomes.

The EAU Paediatric Guidelines Panel conducted a systematic review (SR) assessing the literature from 1980 onwards [694]. The key findings are summarised below.

Due to the heterogeneity of the published literature it was not possible to draw strong conclusions as to whether CAP is superior to observation alone in children diagnosed with antibiotic prophylaxis for antenatal hydronephrosis (ANH). In the first RCT, a prospective longitudinal study [692], female gender, uncircumcised males, lack of CAP, high-grade hydronephrosis, hydroureteronephrosis and VUR were found to be the independent predictors for the development of UTI. The second RCT included in the SR, was published as an abstract only, presented limited data [693]. This trial seemed to focus mainly on patients with ANH and VUR and did not report any beneficial effect of CAP on UTI rates, but details on the study population were limited.

Key findings of the SR are that CAP may or may not be superior to observation in children with antenatal hydronephrosis in terms of decreasing UTI. Due to the low data quality it was also not possible to establish whether boys or girls are at a greater risk of developing a UTI, or ascertain the presence or absence of VUR impacts UTI rates. A correlation between VUR-grade and UTI could not be established either. However, non-circumcised infants, children diagnosed with high-grade hydronephrosis and hydroureteronephrosis were shown to be at higher risk of developing a UTI.

The SR also tried to identify the most effective antibiotic regimen and present data on adverse effects but due to heterogeneity, the available data could not be statistically compared. The most commonly used antibiotic in infants with antenatal hydronephrosis is trimethoprim, but only one study reported side effects [692].

In conclusion, based on the currently available evidence, the benefits and harms of CAP in children with antenatal hydronephrosis remain unproven. Uncircumcised infants and infants with hydroureteronephrosis and high-grade hydronephrosis are more likely to develop a UTI. Continuous antibiotic prophylaxis should be reserved for this sub-group of children who are proven to be at high risk.

#### 3.12.3.2 UPJ obstruction

It is most important that management decisions are made on the basis of serial investigations that have used the same technique and have been performed by the same institution under standardised circumstances.

Symptomatic obstruction (recurrent flank pain, UTI) requires surgical correction using a pyeloplasty, according to the standardised open technique of Hynes and Anderson [695]. In experienced hands, laparoscopic or retroperitoneoscopic techniques and robot-assisted techniques have the same success rates as standard open

procedures. In asymptomatic cases, conservative follow-up is the treatment of choice.

Indications for surgical intervention comprise impaired split renal function (< 40%), a decrease of split renal function of > 10% in subsequent studies, poor drainage function after the administration of furosemide, increased anteroposterior diameter on US, and grade III and IV dilatation as defined by the Society for Fetal Urology [483].

Well-established benefits of conventional laparoscopy over open surgery are the decreased length of hospital stay, better cosmesis, less post-operative pain and early recovery [696, 697]. A recent meta-analysis in children has shown that laparoscopic pyeloplasty (LP) was associated with decreased length of hospital stay and complication rates but prolonged operative time when compared to open pyeloplasty (OP). Additionally, both LP and OP had equal success rates [698]. Robotic-assisted laparoscopic pyeloplasty (RALP) has all the same advantages as LP plus better manoeuvrability, improved vision, ease in suturing and increased ergonomics but higher costs [699, 700]. There does not seem to be any clear benefit of minimal invasive procedures in a very young child but current data is insufficient to defer a cut-off age.

#### 3.12.3.3 Megaureter

The treatment options of secondary megaureters are reviewed in Chapter 3.13.3.

##### 3.12.3.3.1 Non-operative management

If a functional study reveals and confirms adequate ureteral drainage, conservative management is the best option. Initially, low-dose prophylactic antibiotics within the first year of life are recommended for the prevention of UTIs, although there are no existing prospective randomised trials evaluating the benefit of this regimen [701]. With spontaneous remission rates of up to 85% in primary megaureter cases, surgical management is no longer recommended, except for megaureters with recurrent UTIs, deterioration of split renal function and significant obstruction [702].

##### 3.12.3.3.2 Surgical management

In general, surgery is indicated for symptomatic children and if there is a drop in function in conservative follow-up and hydroureteronephrosis is increasing [703]. Data suggest that children with a ureteric diameter of > 10-15 mm are more likely to require intervention [704].

The initial approach to the ureter can be either intravesical, extravesical or combined. Straightening the ureter is necessary without devascularisation. Ureteral tapering should enhance urinary flow into the bladder. The ureter must be tapered to achieve a diameter for an anti-reflux repair. Several tailoring techniques exist, such as ureteral imbrication or excisional tapering [705]. Some institutions perform endoscopic stenting, but there is still no long-term data and no prospective randomised trials to confirm their outcome.

#### 3.12.4 Conclusion

The use of routine perinatal sonography has resulted in increased detection of hydronephrosis caused by UPJ or UVJ obstruction. Meticulous and repeat postnatal evaluation is mandatory to try to identify obstructive cases at risk of renal deterioration and requiring surgical reconstruction. Surgical methods are quite standardised and have a good clinical outcome.

### 3.12.5 Summary of evidence and recommendations for the management of UPJ-, UVJ-obstruction

Summary of evidence	LE
Nowadays, most hydronephrotic kidneys have already been diagnosed prenatally during a maternal US investigation.	2
Ureteropelvic junction obstruction is the leading cause of hydronephrotic kidneys (40%).	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, non-circumcised infants (LE: 1a), children diagnosed with high-grade hydronephrosis (LE: 2) and hydroureteronephrosis (LE: 1b) were shown to be at higher risk of developing UTI.	2

Recommendations	LE	Strength rating
Include serial ultrasound (US) and subsequent diuretic renogram and sometimes voiding cystourethrography in postnatal investigations.	2	Strong
Offer continuous antibiotic prophylaxis to the subgroup of children with antenatal hydronephrosis who are at high risk of developing urinary tract infection like uncircumcised infants, children diagnosed with hydroureteronephrosis and high-grade hydronephrosis, respectively.	2	Weak
Decide on surgical intervention based on the time course of the hydronephrosis and the impairment of renal function.	2	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.	2	Weak
Offer pyeloplasty when ureteropelvic junction obstruction has been confirmed clinically or with serial imaging studies proving a substantially impaired or decrease in function.	2	Weak
Do not offer surgery as a standard for primary megaureters since the spontaneous remission rates are as high as 85%.	2	Strong

### 3.13 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 the level of evidence is generally low. Most of the studies are retrospective, include different patient groups, and have poor stratification of quality. Also, there is 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. The authors have assessed the current literature, but in the absence of conclusive findings, have provided recommendations based on panel consensus. These Guidelines aim to provide a practical approach to the treatment of VUR based on risk analysis.

#### 3.13.1 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 [706]. Vesicoureteric reflux is a very common urological anomaly in children, with an incidence of nearly 1%.

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 over 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 non-symptomatic children has been estimated at 0.4-1.8% [707]. Among infants prenatally identified with hydronephrosis on US, who were screened for VUR, the prevalence was 16.2% (7-35%) [708]. 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%) [708].

However, reflux detected by sibling screening is associated with lower grades [708] and significantly earlier resolution [709]. 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 [710, 711].

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 [712-715].

There is a clear co-prevalence between LUTD and VUR [358]. 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 [358]. Some studies have described a prevalence of 40-60% for VUR in children with LUTD [716]. 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 [717].

The spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical presentation, and anatomy [709]. 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 [717-719].

The presence of renal cortical abnormality, bladder dysfunction, and breakthrough febrile UTIs are negative predictive factors for reflux resolution [720-722].

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 [723-725].

Higher grades of VUR present with higher rates of renal scars. Scar rates vary in different patient groups. In those with prenatal hydronephrosis, renal scarring occurs in 10% of patients [726-731], whereas in patients with LUTD, this may increase up to 30% [725, 732, 733]. 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 [734].

### 3.13.2 **Diagnostic evaluation**

The diagnostic work-up should aim to evaluate the overall health and development of the child, the presence of UTIs, renal status, the presence of VUR, and LUT function. A basic diagnostic work-up comprises 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. The criterion standard in diagnosis of VUR is VCUG, especially at the initial work-up. This test provides precise anatomical detail and allows grading of VUR [735]. In 1985, the International Reflux Study Committee introduced a uniform system for the classification of VUR [736, 737] (Table 7). 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 [737].

Radionuclide studies for detection of reflux have lower radiation exposure than VCUG, but the anatomical details depicted are inferior [738]. Recent studies on alternative imaging modalities for detection on VUR have yielded good results with voiding US and magnetic resonance VCUG [739-741]. 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.

**Table 7: Grading system for VUR on VCUG, according to the International Reflux Study Committee [742]**

<b>Grade I</b>	Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation
<b>Grade II</b>	Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices
<b>Grade III</b>	Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices
<b>Grade IV</b>	Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible
<b>Grade V</b>	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 [743]. Dimercaptosuccinic acid can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis [744]. Children with a normal DMSA scan during acute UTI have a low-risk of renal damage [744].

Video-urodynamic 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 posterior urethral valves. In the case of LUTS, diagnosis and follow-up can be limited to non-invasive tests (e.g. voiding charts, US, or uroflowmetry) [358]. Cystoscopy has a limited role in evaluating reflux, except for infravesical obstruction or ureteral anomalies that might influence therapy.

### 3.13.2.1 *Infants presenting because of prenatally diagnosed hydronephrosis*

Ultrasound of the kidney and bladder is the first standard evaluation tool for children with prenatally diagnosed hydronephrosis. It is non-invasive and provides reliable information regarding kidney structure, size, parenchymal thickness and collecting system dilatation [745, 746].

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 [726, 747]. 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 [708]. 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 [708]. 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 [708, 728, 748, 749]. When infants who are diagnosed with prenatal hydronephrosis become symptomatic with UTIs, further evaluation with VCUG should be considered [749]. Patients with severe hydronephrosis and those whose hydronephrosis is sustained or progressive, need further evaluation to exclude obstruction.

### 3.13.2.2 *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 over-treatment of clinically insignificant VUR. In screened populations the prevalence of VUR is 27.4% in siblings and 35.7% in offspring [742]. 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 [708, 710,

750, 751], screening in all siblings and offsprings 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.

### 3.13.2.3 Recommendations for paediatric screening of VUR

Recommendations	Strength rating
Inform parents of children with vesicoureteric reflux (VUR) that siblings and offspring have a high prevalence of VUR.	Strong
Use renal ultrasound (US) for screening of sibling(s).	Strong
Use voiding cystourethrography if there is evidence of renal scarring on US or a history of urinary tract infection.	Weak
Do not screen older toilet-trained children since there is no added value in screening for VUR.	Weak

### 3.13.2.4 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 the criteria to selecting patients for reflux detection is weak. 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 [752]. 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 carries 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 spot 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 [351, 753-755].

### 3.13.2.5 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 [717, 756]. The co-existence of both conditions should be explored in any patient who has VUR. If there are 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.

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

## 3.13.3 Disease management

There are two main treatment approaches: conservative (non-surgical and surgical).

### 3.13.3.1 Non-surgical therapy

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

- Vesicoureteric reflux resolves spontaneously, mostly in young patients with low-grade reflux. 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 [757].
- Vesicoureteric reflux does not damage the kidney when patients are free of infection and have normal LUT function.
- There is no evidence that small scars can cause hypertension, renal insufficiency or problems during pregnancy. Indeed, these are possible only in cases of severe bilateral renal damage.
- The conservative approach includes watchful waiting, intermittent or continuous antibiotic prophylaxis, and bladder rehabilitation in those with LUTD [732, 756, 758-760].
- 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 [761].



#### 3.13.3.1.1 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. Conservative management should be dismissed in all cases of febrile breakthrough infections, despite prophylaxis, and intervention should be considered.

#### 3.13.3.1.2 Continuous antibiotic prophylaxis

Vesicoureteral reflux increases the risk of UTI and renal scarring especially when in combination with LUTD. Many prospective studies have evaluated the role of continuous antibiotic prophylaxis in the prevention of recurrent UTI and renal scarring.

It is clear that antibiotic prophylaxis may not be needed in every reflux patient [732, 762-764]. Trials show the benefit of CAP is none or minimal in low-grade reflux. Continuous antibiotic prophylaxis is useful in patients with grade III and IV reflux in preventing recurrent infections but its use in preventing further renal damage is not proven. Toilet-trained children and children with LUTD derive much better benefit from CAP [384-387, 765, 766]. 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 [389, 767-769].

It may be difficult and risky to select patients who do not need CAP. 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. Continuous antibiotic prophylaxis is mandatory in patients with LUTD and reflux. Active surveillance of UTI is needed after CAP is discontinued. The follow-up scheme and the decision to perform an anti-reflux procedure or discontinuation of CAP may also depend on personal preferences and the attitude of patients and caregivers. It is strongly advised that the advantages and disadvantages should be discussed in detail with the family.

#### 3.13.3.2 Surgical treatment

Surgical treatment can be carried out by endoscopic injection of bulking agents or ureteral re-implantation.

##### 3.13.3.2.1 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 the distal ureter, 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.

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 (Deflux, Dexell) and more recently polyacrylate-polyalcohol copolymer hydrogel (Vantris) [770, 771].

Although the best results have been obtained with PTFE [772], due to concerns about particle migration, PTFE has not been approved for use in children [773]. Although they are all biocompatible, other compounds such as collagen and chondrocytes have failed to provide a good outcome. Deflux was approved by the USA FDA in 2001 for the treatment of VUR in children. Initial clinical trials have demonstrated that this method is effective in treating reflux [774]. Studies with long-term follow-up have shown that there is a high recurrence rate which may reach as high as 20% in two years [762].

In a meta-analysis [775] 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%) vs. single (73%) systems, and neuropathic (62%) vs. normal (74%) bladders.

Clinical validation of the effectiveness of anti-reflux 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%) [776]. Longer follow-up studies are needed to validate these findings.

#### 3.13.3.2.2 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%) [777].

The most popular and reliable open procedure is cross trigonal re-implantation described by Cohen. The main concern with this procedure is the difficulty of accessing the ureters endoscopically if needed when the child is older. Alternatives are suprahiatal re-implantation (Politano-Leadbetter technique) and infrahiatal re-implantation (Glenn-Anderson technique). If an extravesical procedure (Lich-Gregoir) is planned, cystoscopy should be performed pre-operatively to assess the bladder mucosa and the position and configuration of the ureteric orifices. In bilateral reflux, an intravesical anti-reflux procedure may be considered, because simultaneous bilateral extravesical reflux repair carries an increased risk of temporary post-operative urine retention [778]. Overall, all surgical procedures offer very high and similar success rates for correcting VUR.

#### 3.13.3.2.3 Laparoscopy and robot-assisted

There have been a considerable number of case series of transperitoneal, extravesical and pneumovesicoscopic intravesical ureteral re-implantation, which have shown the feasibility of the techniques. Various anti-reflux surgeries have been performed with 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, further studies are needed to define the success rates, costs and benefits of this minimal invasive approach [779, 780].

The major shortcoming of the new techniques seems to be the longer operative times, which hinder their wider acceptance. Also, 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. It can be offered as an alternative to the caregivers in centres where there is established experience [761, 780-788].

### 3.13.4 **Summary of evidence and recommendations for the management of vesicoureteric reflux in childhood**

<b>Summary of evidence</b>
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 different risk groups.
Surgical correction should be considered in patients with persistent high-grade reflux (grades IV/V). There is no consensus about the timing and type of surgical correction. The outcome of open surgical correction 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
Initially treat all patients diagnosed within the first year of life 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
Offer definitive surgical or endoscopic correction to patients with frequent breakthrough infections.	Weak
Offer open surgical correction to patients with persistent high-grade reflux and endoscopic correction for lower grades of reflux.	Strong
Initially manage all children presenting at age one to five years conservatively.	Strong
Offer surgical repair to children above the age of one presenting with high-grade reflux and abnormal renal parenchyma.	Weak
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 done in all and especially in children after toilet-training. If LUTD is found, the initial treatment should always be for LUTD.	Strong
Offer surgical correction, if parents prefer definitive therapy to conservative management.	Strong
Select the most appropriate management option based on : <ul style="list-style-type: none"> <li>• the presence of renal scars;</li> <li>• clinical course;</li> <li>• the grade of reflux;</li> <li>• ipsilateral renal function;</li> <li>• bilaterality;</li> <li>• bladder function;</li> <li>• associated anomalies of the urinary tract;</li> <li>• age and gender;</li> <li>• compliance;</li> <li>• parental preference.</li> </ul> Refer to Table 8 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 8: Management and follow-up according to different 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 6 months
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grade IV-V), abnormal kidneys and no LUTD	Intervention should be considered	Open surgery has better results than endoscopic surgery	Post-operative VCUG on indication only; follow-up of kidney status until after puberty
Moderate	Symptomatic male or female patients before toilet-training, with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT infections or persistent reflux	Spontaneous resolution is higher in males	Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months

Moderate	Asymptomatic patients (PNH or sibling) with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT, infections or persistent reflux		Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months
Moderate	Symptomatic male or female patients after toilet-training, with high-grade reflux and normal kidneys with LUTD	Initial treatment is always for LUTD with CAP. Intervention may be considered in cases of BT infections or persistent reflux	In case of persistent LUTD, despite urotherapy, intervention should be considered. The choice of intervention is controversial	Follow-up for UTI and LUTD, kidney status; full re-evaluation after successful urotherapy
Moderate	Symptomatic male or female patients after toilet-training with low-grade reflux, abnormal kidneys with or without LUTD	Choice of treatment is controversial. Endoscopic treatment may be an option. LUTD treatment should be given if needed		Follow-up for UTI, LUTD, and kidney status until after puberty
Moderate	All symptomatic patients with normal kidneys, with low-grade reflux, with LUTD	Initial treatment is always for LUTD with or without CAP		Follow-up for UTI and LUTD
Low	All symptomatic patients with normal kidneys, with low-grade reflux, with no LUTD	No treatment or CAP	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI
Low	All asymptomatic patients with normal kidneys with low-grade reflux	No treatment or CAP in infants	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI

BT = breakthrough; CAP = continuous antibiotic prophylaxis; LUTD = lower urinary tract dysfunction; PNH = prenatal diagnosed hydronephrosis; UTI = urinary tract infection; VCUG = voiding cystourethrography.

### 3.14 Urinary stone disease

#### 3.14.1 *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. Obtaining a stone-free state with close follow-up are of the utmost importance, 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 [789]. Patients with augmented bladder constitute another important group with a risk of up to 15% [790].

The incidence and characteristics of stones show a wide geographical variation in children. Although urinary stone disease is generally considered to be a relatively rare disease, it is quite common in some parts of the world. Paediatric stone disease is endemic in Turkey, Pakistan and in some South Asian, African and South American states. However, recent epidemiological studies have shown that the incidence of paediatric stone disease is also increasing in the Western world [791-793], especially in girls, Caucasian ethnicity, African Americans and older children [794]. More than 70% of stones in children contain calcium oxalate, while infection stones are found more frequently in younger children [795].

#### 3.14.2 *Classification systems*

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

### 3.14.2.1 Calcium stones

Calcium stones are usually made from calcium oxalate or calcium phosphate. Super-saturation 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.

*Hypercalciuria:* This is defined by a 24-hour urinary calcium excretion of more than 4 mg/kg/day (0.1 mmol/kg/day) in a child weighing < 60 kg. In infants younger than three months, 5 mg/kg/day (0.125 mmol/kg/day) is considered to be the upper limit for normal calcium excretion [796].

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 (hypercalcemic) hypercalciuria, a high serum calcium level may be due to increased bone resorption (hyperparathyroidism, hyperthyroidism, immobilisation, acidosis, metastatic disease) or gastrointestinal hyperabsorption (hypervitaminosis D) [797].

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 [796, 797]. 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 4 mg/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 [796-799]. 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 assess accurately the daily intake of calcium, animal protein, and sodium. Dietary sodium restriction is recommended as well as maintenance of calcium intake consistent with the daily needs of the child [800]. 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 [801] (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 0.5-1 mg/kg/day [802-805] (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 with regular intervals. Citrate therapy is also useful if citrate levels are low or if hypercalciuria persists, despite other therapies [802, 806] (LE: 4).

*Hyperoxaluria:* Only 10-15% of oxalate comes from diet.

The average child excretes less than 50 mg (0.57 mmol)/1.73 m<sup>2</sup>/day [807-809], 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 in resulting deposition of calcium oxalate in other tissues (oxalosis). The diagnosis is made upon laboratory findings of severe hyperoxaluria and clinical symptoms. The definitive diagnosis requires liver biopsy to assay the enzyme activity.

Other forms of hyperoxaluria, as mentioned earlier, may be due to hyperabsorption of oxalate in inflammatory bowel syndrome, pancreatitis and short bowel syndrome. Yet, the majority of children have 'mild' (idiopathic) hyperoxaluria, with urine oxalate levels elevated only mildly in these cases. The treatment of hyperoxaluria consists of the promotion of high urine flow, restriction of dietary oxalate and regular calcium intake. Pyridoxine may be useful in reducing urine levels, especially in primary hyperoxaluria. Citrate administration increases inhibitory urine activity [802, 810] (LE: 4).

Hypocitraturia: Citrate is a urinary stone inhibitor. Citrate acts by binding to calcium and by directly inhibiting the growth and aggregation of calcium oxalate as well as calcium phosphate crystals. Thus low urine citrate may be a significant cause of calcium stone disease. In adults, hypocitraturia is the excretion of citrate in urine of less than 320 mg/day (1.5 mmol/day) for adults; this value must be adjusted for children depending on body size [811-813].

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 [812, 814].

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 1 mEq/kg, given in two divided doses [813] (LE: 3). 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 hyperkalemic and chronic renal failure conditions.

#### 3.14.2.2 *Uric acid stones*

Uric acid stones are responsible for urinary calculi in 4-8% of children. Uric acid is the end product of purine metabolism. Hyperuricosuria is the main cause of uric acid stone formation in children. A daily output of uric acid of more than 10 mg/kg/day (0,6 mmol/kg/day) is considered to be hyperuricosuria [802].

The formation of uric acid stones is mainly dependent on the presence of acidic urinary composition. Uric acid dissociation and solubility is strongly reduced at 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, it can be caused by uric acid overproduction secondary to inborn errors of metabolism, myeloproliferative disorders or other causes of cell breakdown. Hyperuricosuria is also caused by high purine and protein intake. Although hyperuricosuria is a risk factor for calcium oxalate stone formation in adults, this does not appear to be a significant risk factor in children.

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

Alkalinisation of urine is the mainstay of therapy and prevention for uric acid stones. Citrate preparations are useful as alkalinising agents. Maintaining a urine pH of 6 to 6.5 is sufficient to prevent uric acid stones [802]. In cases who failed with conservative measures with sustaining hyperuricosuria and hyperuricemia, stone recurrences or myeloproliferative diseases, allopurinol (10 mg/kg) may be used. This medication may cause several drug reactions (rash, diarrhoea, eosinophilia) and should be cautiously used in chronic renal failure patients.

#### 3.14.2.3 *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, so leading to the formation of mixed-composition stones. Cystine stones are faintly radiopaque and may be difficult to visualise on regular radiograph studies. They are also hard in texture and more difficult to disintegrate by extracorporeal shockwave lithotripsy (SWL).

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 alphamercaptopropionyl glycine or D-penicilamin 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 [815] (LE: 4).

#### 3.14.2.4 *Infection stones (struvite stones)*

Infection-related stones constitute nearly 5% of urinary stones in children, though incidence increases over

10% in younger ages [816] and in non-endemic regions [795, 817]. 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 treatment, as stones will harbour infection and antibiotic treatment will not be effective. Consideration should be given to investigating any congenital problem that causes stasis and infection. Genitourinary tract anomalies predispose to formation of such stones.

### 3.14.3 **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, non-visible 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 [818, 819].

#### 3.14.3.1 *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 [820-822] (LE: 2). Despite its high diagnostic accuracy, because of the potential radiation hazards, its use should be reserved for cases with non-informative US and/or plain abdominal roentgenogram. Low dose protocols have also been developed with the goal of reducing radiation dose with adequate image quality [823]. Intravenous pyelography is rarely used in children, but may be needed to delineate the caliceal anatomy prior to percutaneous or open surgery.

#### 3.14.3.2 *Metabolic evaluation*

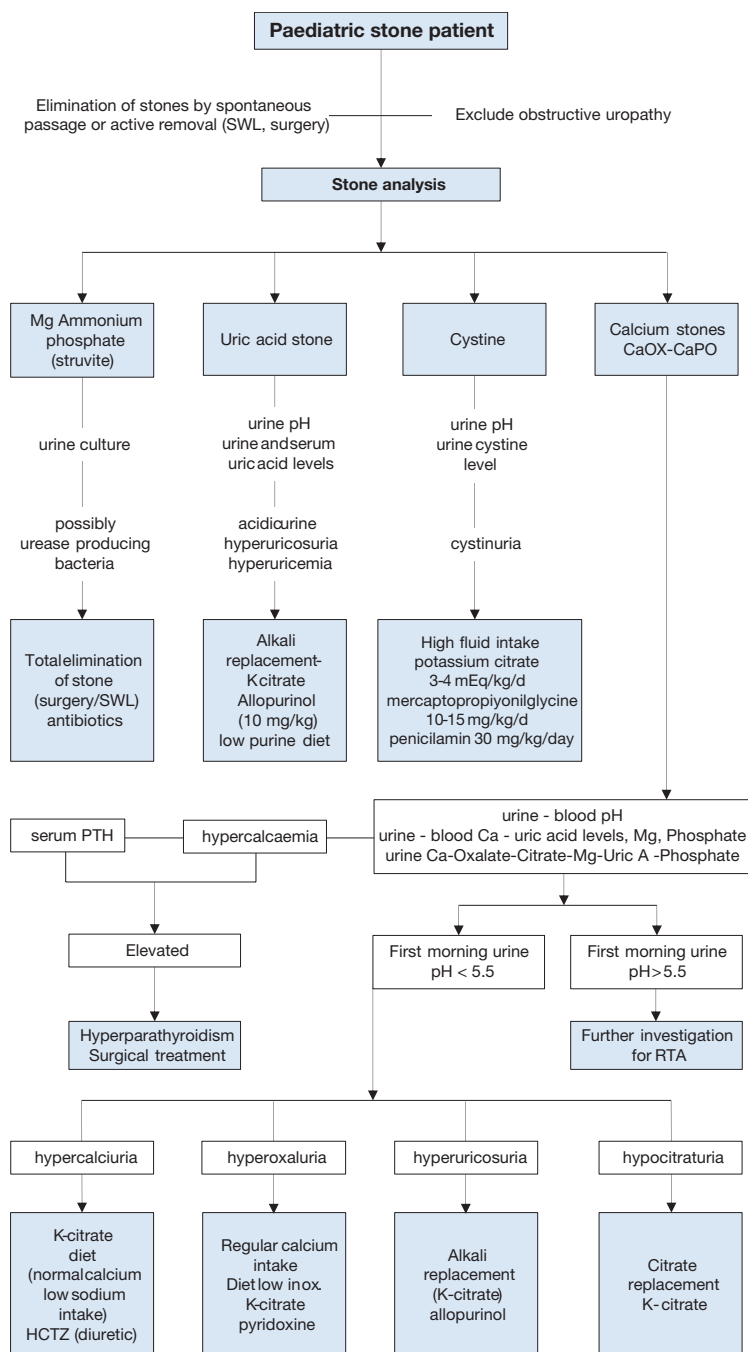
Due to the high incidence of predisposing factors for urolithiasis in children and high stone recurrence rates, every child with a urinary stone should be given a complete metabolic evaluation [789, 824-826].

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 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;
- 24-hour cystine analysis if cystinuria is suspected (positive sodium nitroprusside test, cystine stone, cystine hexagonal crystals in urine).

Figure 8 provides an algorithm of how to perform metabolic investigations in urinary stone disease in children and how to plan medical treatment accordingly.

**Figure 8: Algorithm for metabolic investigations in urinary stone disease in children**



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

### 3.14.4 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 [825, 827, 828]. Expectant management is the initial management in children with asymptomatic small size stones (< 4-5 mm) with a possibility of spontaneous clearance. 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  $\alpha$ -blockers. Although, experience in children is limited showing different results [829], a recent 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 [830]. Currently, most paediatric



stones can easily be managed by SWL. Endoscopic treatment can be applied for ureteric and bladder stones. Percutaneous removal of stones is also possible for kidney stones in children. Only a small portion of children will require open surgery but all attempts must be made to completely remove all stones since post-operative residual fragments pass spontaneously in only 20-25% of cases [831, 832]. A congenital obstructive uropathy should be managed together with stone removal therapy to prevent recurrence.

#### 3.14.4.1 *Extracorporeal shockwave lithotripsy*

Many reports confirm that SWL can be performed in children with no suspicion of long-term morbidity of the kidney [833-840].

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 14 kV and 21 kV. 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 [827, 841, 842]. Concerns about anaesthesia no longer present a problem due 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 co-operate [843] (LE: 2b).

Stone-free rates are significantly affected by various factors. Regardless of the location, as the stone size increases, the stone-free rates decrease and retreatment rate increases. The stone-free rates for < 1 cm, 1-2 cm, > 2 cm and overall, were reported as nearly 90%, 80%, 60% and 80%, respectively. As the stone size increases, the need for additional sessions increases [827, 841, 842, 844-848].

Localisation of the calculi has been described as a significant factor affecting the success rates in different studies. Stones in the renal pelvis and upper ureter seem 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% [849-852].

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 [850-854].

The type of machine used has a strong effect on success rates and complications. First-generation machines can deliver more energy to a larger focal zone, resulting in higher fragmentation rates in a single therapy. However, general anaesthesia is usually required due to the intolerable discomfort associated with a first-generation machine. Later-generation machines have a smaller focal zone and deliver less energy, and have a lower risk of pulmonary trauma, however, additional treatments may be needed. The success rate is higher in younger children [846].

Although stenting does not affect stone clearance, overall complication rates are higher and hospital stay is longer in the unstented patient [846, 848]. 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 prolonged obstruction [826, 845].

The Hounsfield Unit (HU) of stone on noncontrast 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 less than 600 [832] and 1,000 [855]. Two nomogram studies revealed male gender, younger age, smaller stone size, single stone, non-lower pole localisation and negative history for previous intervention are favourable factors for stone clearance in paediatric SWL [856, 857].

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;
- rarely, haemoptysis.

In children with sterile pre-operative urine cultures, antibiotic prophylaxis to decrease infectious complications is not recommended [858]. However, every effort should be made to sterilise the urine before performing SWL, ureteroscopy (URS), or percutaneous nephrolithotomy (PCNL).

Due to the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [859-868].

#### 3.14.4.2 Percutaneous nephrolithotomy (PCNL)

Shockwave lithotripsy is the first choice for treating most renal paediatric stones. However, percutaneous renal surgery should be used for larger and complex stones. Pre-operative 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 means that PCNL can be used in children. In children (particularly smaller children), PCNL has some advantages, such as smaller skin incision, single-step dilation and sheath placement, good working access for paediatric instruments, variable length, and lower cost [858, 869, 870].

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 [862, 871-875].

The most frequently reported complications of PCNL in children are bleeding, post-operative fever or infection, and persistent urinary leakage. Bleeding requiring transfusion in the modern series is reported in less than 10% [876-881] and is closely associated with stone burden, operative time, sheath size and the number of tracts [880, 882, 883]. In recent studies, post-operative infectious complications, such as fever with or without documented UTI, are reported as less than 15% [876, 877, 879-881, 884] and the origin of fever is not always found to be the infection. With the availability of smaller size instruments, miniaturised PCNL ('miniperc') through a 13F or 14F sheath [870, 885, 886] as well as ultramini-PCNL (UMP) through 12F sheaths [887] have become possible, with decreased transfusion rates [885]. This miniaturisation has been further developed into the technique of 'micro-perc' using a 4.85F 'all-seeing needle'. This technique is still experimental and enables the stone to be fragmented by a laser *in situ* and left for spontaneous passage [888]. A recent study revealed that microperc provides a similar stone-free rate with similar complication rates and a lower additional treatment rate compared with SWL in the treatment of kidney stone disease in children [889] (LE: 3). For stones 10-20 mm, micro-PNL was shown to have comparable results, with lesser bleeding, compared to mini-PCNL [890] (LE: 3). As experience has accumulated in adult cases, new approaches have also started to be applied in children, including tubeless PCNL. This technique has been used in uncomplicated surgery for stones < 2 cm, with patients left either with an indwelling catheter or double J stent in the ureter [878, 884] or totally tubeless [891]. Moreover, use of US for establishment of access [892] and supine approach [893] were also reported to be feasible in children.

The mean post-operative hospital stay is similar to adults. It is reported as three to four days in all published literature and is much shorter than open surgery. The less invasive nature of this technique has made it a promising alternative to open surgery for treating renal stones in children (LE: 2) [876, 878, 879, 881-884, 886-893].

#### 3.14.4.3 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. It is strongly recommended that guide wires are used and the procedure is performed using direct vision. Routine balloon dilation of ureterovesical junction and ureteral stenting are controversial. In general, ureteric dilatation is being performed much less and only in selected cases. There is a tendency to use hydrodilation more because it is similarly effective [858, 860, 866, 894-897] (LE: 3).

Different 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 [859-868].

All studies reporting the use of endoscopy for ureteric stones in children have clearly demonstrated that there is no significant risk of ureteric strictures or reflux with this mode of therapy (LE: 1). The risk of post-operative hydronephrosis depends on the presence of impacted stone and ureteral injury during operation [898]. A multi-institutional study on the use of semi-rigid ureteroscopy for ureteral calculi in children has revealed that the procedure is effective with a 90% stone-free rate 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 [899].

A recent 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 [900-904]. In these series, the authors generally did not use active orifice dilation, but attempted to use a ureteral sheath where possible. However, an important problem was the inability to obtain retrograde access to the ureter in approximately half of the cases [901, 903]. 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 [900, 902-905]. The need for additional procedures was related to stone size [904]. A comparative study showed that retrograde intra-renal surgery (RIRS) had similar stone-free rate compared to ESWL after three months, with fewer sessions [906], however for stones larger than 2 cm, RIRS monotherapy has lower stone-free rates than mini-PCNL with the advantages of decreased radiation exposure, fewer complications and shorter hospital stay [907] (LE: 3). On the other hand, for stones between 10-20 mm, RIRS has similar success and complication rates and shorter hospital stay and low radiation exposure when compared to micro-PNL [908] (LE: 3).

#### 3.14.4.4 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 require surgical correction. Open surgery is also necessary in children with severe orthopaedic deformities that limit positioning for endoscopic procedures.

In centres with a 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 previous failed endoscopic procedures, complex renal anatomy (ectopic or retrorenal colon), concomitant ureteropelvic junction (UPJ) obstruction or caliceal diverticula, megaureter, or large impacted stones. Laparoscopic stone surgery via conventional or a robot-assisted transperitoneal or retroperitoneal approach can be attempted. However, there is very limited experience with these techniques and they are not routine therapeutic modalities [909-912].

Bladder stones in children can usually be managed by endoscopic techniques. Open surgery may also be used for very large bladder stones or for bladder stones caused by an anatomical problem.

In addition to the advantages and disadvantages of each treatment modality for the specific size and location of the stone, one will have to consider the availability of the instruments and the experience with each treatment modality before the choice of technique is made. Recommendations for interventional management are given in Table 9.

**Table 9: Recommendations for interventional management in paediatric stones**

Stone size and localisation*	Primary treatment option	Secondary treatment options	Comment
Staghorn stones	PCNL	Open/SWL	Multiple sessions and accesses with PCNL may be needed. Combination with SWL may be useful.
Pelvis < 10 mm	SWL	RIRS/PCNL/MicroPerc	
Pelvis 10-20 mm	SWL	PCNL/RIRS/MicroPerc/Open	Multiple sessions with SWL may be needed. PCNL has similar recommendation grade.
Pelvis > 20 mm	PCNL	SWL/Open	Multiple sessions with SWL may be needed.
Lower pole calyx	PCNL	SWL/Open	Multiple sessions with SWL may be needed.
< 10 mm	SWL	RIRS/PCNL/MicroPerc	Anatomical variations are important for complete clearance after SWL.
Lower pole calyx	SWL	RIRS/PCNL/MicroPerc	Anatomical variations are important for complete clearance after SWL.
> 10 mm	PCNL	SWL/ MicroPerc	Anatomical variations are important for complete clearance after SWL.
Upper ureteric stones	SWL	PCNL/URS/Open	
Lower ureteric stones	URS	SWL/Open	Additional intervention need is high with SWL.

Bladder stones	Endoscopic		Open is easier and with less operative time with large stones.
Bladder stones	Endoscopic		Open is easier and with less operative time with large stones.

\* Cystine and uric acid stones excluded.

PCNL = percutaneous nephrolithostomy; SWL = shockwave lithotripsy; RIRS = retrograde intrarenal surgery; URS = ureteroscopy.

### 3.14.5 Summary of evidence and recommendations for the management of urinary stones

Summary of evidence	LE
The incidence of stone disease in children is increasing.	2
Contemporary surgical treatment is based on minimally invasive modalities. Open surgery is very rarely indicated.	2a
The term 'clinically insignificant residual fragments' is not appropriate for children since most of them become symptomatic and require intervention.	2b

Recommendations	LE	Strength rating
Use plain abdominal X-ray and ultrasound as the primary imaging techniques for the diagnosis and follow-up of stones.	2b	Strong
Use low-dose non-contrast computed tomography in cases with a doubtful diagnosis, especially of ureteral stones or complex cases requiring surgery.	2a	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.	2a	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.	2a	Strong

## 3.15 Obstructive pathology of renal duplication: ureterocele and ectopic ureter

### 3.15.1 Epidemiology, aetiology and pathophysiology

Ureterocele and ectopic ureter are the two main anomalies associated with complete renal duplication, but they also occur in a single system. At present, antenatal US detects both conditions in the majority of cases if associated with obstruction, and diagnosis is confirmed after birth by further examination. Later in life, these anomalies are revealed by clinical symptoms: UTI, pain, calculus formation, disturbances of micturition, and urinary incontinence. There is a wide variation of symptoms in patients with ureterocele (from the asymptomatic patient to urosepsis, urinary retention and upper tract dilatation after birth).

#### 3.15.1.1 Ureterocele

Ureterocele is four to seven times more frequent in female than in male patients; the overall incidence in autopsies is around one in 4,000 children. Around 80% is associated with the upper pole ureter in duplicated systems and 20% in single systems. About 10% of ureteroceles are bilateral [913].

#### 3.15.1.2 Ectopic ureter

Ectopic ureter is less frequent than ureterocele (10 in 19,046 autopsies), but is also more common in female patients (male to female ratio is 1:5). Some remain asymptomatic, therefore, the true incidence is difficult to determine [914]. Eighty per cent of ectopic ureters are associated with complete renal duplication; however, in male patients about 50% of ectopic ureters are associated with a single system [915].

### 3.15.2 Classification systems

#### 3.15.2.1 Ureterocele

Ureterocele is a cystic dilatation that develops in the intravesical part of the submucosal ureter. The aetiology remains unclear [916-918]. A single-system ureterocele is associated with a kidney with one ureter, and in duplex systems, the ureterocele belongs to the upper pole.

Ureteroceles usually cause obstruction of the upper pole, but the degree of obstruction and functional impairment is variable according to the type of ureterocele and upper pole dysplasia. In the

orthotopic form, there is often no or only mild obstruction, and frequently the function of the moiety is normal or slightly impaired, and the corresponding ureter may be dilated. Cystic renal dysplasia is also associated with a single system ureterocele [919]. Vesicoureteral reflux can be observed in 50% on the ipsilateral side and 20% on the contralateral side. Reflux into the ureterocele is uncommon [920]. In the ectopic form, the upper pole is altered, frequently dysplastic, and hypo-functional or non-functional [921, 922]. The corresponding ureter is a mega-ureter. In the caeco-ureterocele (see definition below), the upper pole of the renal duplication is dysplastic and non-functional. Histological evaluation demonstrated that the changes represent a process of maldevelopment and may not result from infections or obstruction [921].

#### 3.15.2.1.1 Ectopic (extravesical) ureterocele

If any portion of the ureterocele extends into the bladder neck or urethra, it is called an ectopic ureterocele. Ectopic ureterocele is the most common form of ureterocele (> 80%). It can be voluminous, dissociating the trigone and slipping into the urethra, and may prolapse through the urethral meatus (caeco-ureterocele). The ureterocele orifice is tight, and located in the bladder itself or below the neck. The ureter corresponding to the lower pole moiety is raised by the ureterocele and is frequently refluxing or compressed by the ureterocele, leading to an obstructive mega-ureter. A contralateral renal duplication is associated with 50% of cases. Occasionally, large ureteroceles are responsible for reflux or obstruction of the contralateral upper tract.

#### 3.15.2.1.2 Orthotopic (intravesical) ureterocele

The intravesical or orthotopic ureterocele is completely located in the bladder. Intravesical ureteroceles are mostly combined with a single kidney system and account for about 15% of cases. It is diagnosed more in older children or adults.

#### 3.15.2.2 Ectopic ureter

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 pole 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 [923]:

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

In boys, the ureteral orifice may be located [923]:

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

### 3.15.3 **Diagnostic evaluation**

#### 3.15.3.1 Ureterocele

Prenatal US easily reveals voluminous obstructive ureteroceles [924]. In cases with a small upper pole or a slightly obstructive ureterocele, prenatal diagnosis is difficult.

If prenatal diagnosis is impossible, 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 a newborn boy, it might cause acute urinary retention, simulating urethral valves.
- The early symptom of pyelonephritis in either sex may lead to the diagnosis.
- Later symptoms can include dysuria, recurrent cystitis and urgency.

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

At this point, it is important to assess the function of the upper pole using nuclear renography of the region of interest. This is best assessed with DMSA, however this requires a careful systematic review of the images [925]. Magnetic resonance urography may visualise the morphological status of the upper pole and lower moieties and of the contralateral kidney as well as it can detect renal scars [926, 927]. Using functional MR urography, differential renal function can be assessed with a quite low intra- and interobserver variability [928]. Based on the prevalence of high-grade reflux, VCUG is mandatory for identifying

ipsilateral or contralateral reflux and assessing the degree of intra-urethral prolapse of the ureterocele [929]. Urethrocystoscopy may reveal the pathology in cases where it is difficult to make the differential diagnosis between ureterocele and ectopic mega-ureter.

#### 3.15.3.2 Ectopic ureter

Most of the ectopic mega-ureters are diagnosed primarily by US. In some cases, clinical symptoms can lead to diagnosis:

- In neonates: dribbling of urine, pyuria, and acute pyelonephritis.
- In young girls: permanent urinary incontinence besides normal voiding, or significant vaginal discharge as the equivalent of incontinence; an ectopic orifice may be found in the meatal region [930].
- In pre-adolescent boys: epididymitis is the usual clinical presentation and the seminal vesicle may be palpable.

Ultrasound, radionuclide studies (DMSA, VCUG, MR urography, high-resolution MRI, and cystoscopy) are the diagnostic tools to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction [931]. In some cases, the large ectopic ureter presses against the bladder and can look like a pseudo-ureterocele [932].

Girls who present with lifelong minimal urinary incontinence, never being dry, normal bladder function, complete emptying, and normal US are very suspicious for ectopic ureter. This needs to be excluded or confirmed by MRI as it is the most sensitive method [933].

### 3.15.4 **Management**

#### 3.15.4.1 *Ureterocele*

Management is controversial with a choice between a non-operative approach, endoscopic decompression, ureteral re-implantation, partial nephroureterectomy, or complete primary reconstruction [934-938]. 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 pole; 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 [939]. When the diagnosis is made by US, prophylactic antibiotic treatment maybe indicated until a VCUG is performed.

##### 3.15.4.1.1 Early treatment

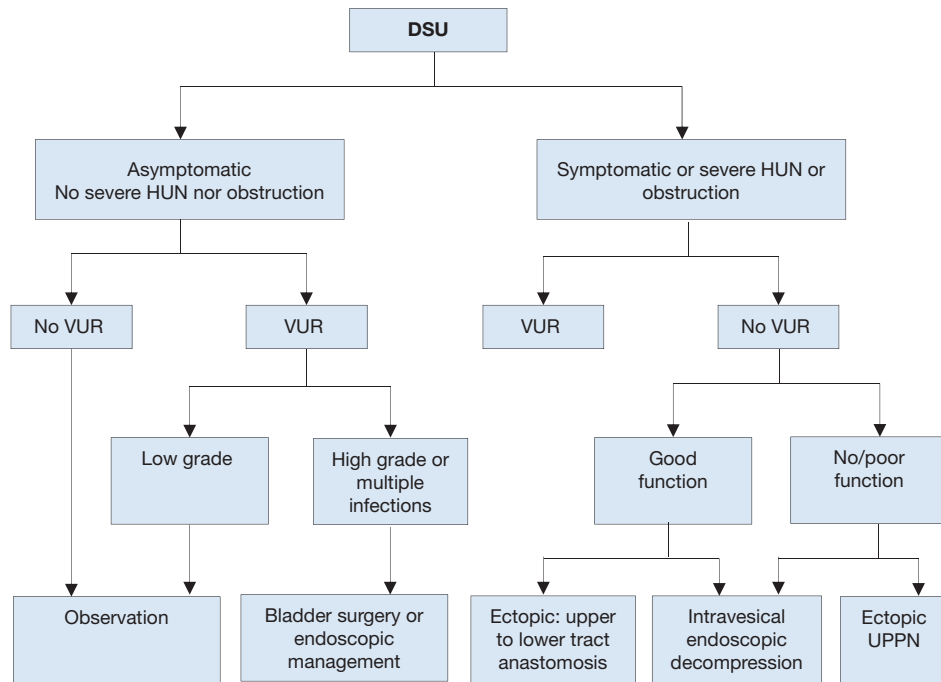
In the presence of febrile infection or obstruction at the bladder neck, immediate endoscopic incision or puncture of the ureterocele is recommended. In a clinically asymptomatic child with a ureterocele and a non or hypofunctional upper pole, without significant obstruction of the lower pole and without bladder outlet obstruction, prophylactic antibiotic treatment is given until follow-up procedures are instigated. Decompression of the dilated system facilitates later reconstructive surgery [940, 941].

##### 3.15.4.1.2 Re-evaluation

Conservative treatment may be adopted in asymptomatic patients without any bladder outlet obstruction, severe hydronephrosis of the ureterocele moiety or high-grade (over grade III) reflux [939, 942]. A meta-analysis showed that, after primary ureterocele-incision, the re-operation rate is higher in those with an ectopic ureterocele compared to those with an intravesical ureterocele [935]. Secondary surgery is necessary if decompression is not effective, significant reflux is present, or there is obstruction of the ipsi- or contralateral ureters, and/or bladder neck obstruction or retained ureterocele [943].

Surgery may vary from upper pole nephrectomy to complete unilateral LUT reconstruction [938, 944-946]. In an ectopic ureterocele with severe hydronephrosis and without reflux, the primary upper tract approach without endoscopic decompression (partial upper-pole nephroureterectomy, pyelo/ureteropyelo/ureterostomy and upper-pole ureterectomy) has an 80% chance of being the definitive treatment [939, 947]. Also a LUT approach in those with a poorly or non-functioning upper pole is an option [948]. Today, despite successful surgery, some authors think, that surgery may not be necessary at all in some patients [949], as less aggressive surgical treatment and non-operative management over time can achieve the same functional results [950].

**Figure 9: Algorithm for the management of duplex system ureterocele after the first 3-6 months of life**  
[939]



DSU = duplex system ureterocele; HUN = hydroureteronephrosis; UPPN = upper pole partial nephrectomy; VUR = vesicoureteric reflux to the lower pole.

Obstruction is considered to be the presence of non-refluxing dilatation of non-ureterocele-bearing moieties (especially of the lower pole) or of an obstructive drainage pattern on diuretic renography.

#### 3.15.4.2 Ectopic ureter

In the majority of cases, the upper pole is dysplastic and poorly functioning. There is a variety of therapeutic options, each with its advantages and disadvantages. In non-functioning moieties with recurrent infections, heminephro-ureterectomy is a definite solution. Ureteral reconstruction (ureteral re-implantation/ ureteroureterostomy/ureteropyelostomy and upper-pole ureterectomy) are other therapeutic options especially in cases in which the upper pole has function worth preserving. These procedures can be performed through an open laparoscopic or robotic assisted approach [951-954]. So far there is no superior approach [955]. In patients with bilateral single ectopic ureters (a very rare condition), an individual approach depending on the sex and renal and bladder function of the patient is necessary. Usually the bladder neck is insufficient in these patients [956].

#### 3.15.5 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 associated with complete renal duplication, but they also occur in a single system.	1
In most cases, in young children (first years of life) diagnosis is done by US.	1
In older children clinical symptoms will prompt assessment.	1
Management includes a conservative approach, endoscopic decompression, partial nephroureterectomy, or complete primary reconstruction. Choice of treatment will depend on: <ul style="list-style-type: none"> <li>clinical status of the patient (e.g., urosepsis);</li> <li>patient age;</li> <li>function of the upper pole;</li> <li>presence of reflux or obstruction of the ipsilateral or contralateral ureter;</li> <li>presence of bladder neck obstruction caused by ureterocele;</li> <li>intravesical or ectopic ureterocele;</li> <li>and caregivers' and surgeon's preferences.</li> </ul>	3

Recommendations			LE	Strength rating
Ureterocele	Diagnosis	Use ultrasound (US), radionuclide studies (mercaptoacetyltriglycine (MAG3)/dimercaptosuccinic acid (DMSA)), voiding cystourethrography (VCUG), magnetic resonance urography, high-resolution magnetic resonance imaging (MRI), and cystoscopy to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction.	3	Weak
	Treatment	Select treatment based on symptoms, function and reflux as well on surgical and parenteral choices: observation, endoscopic decompression, ureteral re-implantation, partial ephroureterectomy, complete primary reconstruction.	3	Weak
		Offer, early endoscopic decompression to patients with an obstructing ureterocele.		
Ectopic ureter	Diagnosis	Use US, DMSA scan, VCUG or MRI for a definitive diagnosis.	3	Weak
	Treatment	In non-functioning moieties with recurrent infections, heminephro-ureterectomy is a definitive solution. Ureteral reconstruction (ureteral re-implantation/ureteroureterostomy/ureteropyelostomy and upper-pole ureterectomy) are other therapeutic option especially in cases in which the upper pole has function worth preserving.	3	Weak

### 3.16 Disorders of sex development

#### 3.16.1 *Epidemiology, aetiology and pathophysiology*

The formerly called 'intersex disorders' were recently the subject of a consensus document in which it was decided that the term 'intersex' should be changed to 'disorders of sex development' (DSD) [957, 958].

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

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

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

Disorders of sex development can present as prenatal diagnosis, neonatal diagnosis and late diagnosis. Prenatal diagnosis can be based on karyotype or US findings, neonatal diagnosis is based on genital ambiguity and late diagnosis is made on early or delayed puberty. In this guideline focus is on the neonatal presentation where the paediatric urologist plays a major role. For late diagnosis we refer to endocrinology and gynaecology guidelines on precocious and delayed puberty where paediatric urologists play a minor role [959, 960].

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

##### 3.16.1.1 *Micropenis*

Micropenis is a small but otherwise normally formed penis with a stretched length of < 2.5 standard deviation below the mean [957, 958, 961].



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

- hypogonadotropic hypogonadism (due to an inadequate secretion of GnRH);
- hypergonadotropic hypogonadism (due to failure of the testes to produce testosterone).

The penis is measured on the dorsal aspect, while stretching the penis, from the pubic symphysis to the tip of the glans [958]. The corpora cavernosa are palpated, the scrotum is often small, and the testes may be small and descended. Micropenis should be distinguished from buried and webbed penis, which is usually of normal size. The initial evaluation has to define whether the aetiology of the micropenis is central (hypothalamic/pituitary) or testicular. A paediatric endocrinology work-up has to be carried out immediately. Karyotyping is mandatory in all patients with a micropenis. Endocrine testicular function is assessed (baseline and stimulated testosterone, luteinising hormone (LH) and follicle-stimulating hormone (FSH) serum levels). Stimulated hormone levels may also give an idea of the growth potential of the penis. In patients with non-palpable testes and hypogonadotropic hypogonadism, laparoscopy should be carried out to confirm vanishing testes syndrome or intra-abdominal undescended hypoplastic testes. This investigation can be delayed until the age of one year [957].

Pituitary or testicular insufficiency are treated by the paediatric endocrinologist. In patients with testicular failure and proven androgen sensitivity, androgen therapy is recommended during childhood and at puberty to stimulate the growth of the penis [962-965] (LE: 2). In the presence of androgen insensitivity, good outcome of sexual function is questioned and gender conversion can be considered [966-968].

### 3.16.2 **Diagnostic evaluation**

#### 3.16.2.1 *The neonatal emergency*

The first step is to recognise the possibility of DSD (Table 10) and to refer the newborn baby immediately to a tertiary paediatric centre, fully equipped with neonatal, genetics, endocrinology and paediatric urology units. At the paediatric centre, the situation should be explained to the caregivers fully and kindly. Registering and naming the newborn should be delayed as long as necessary.

##### 3.16.2.1.1 Family history and clinical examination

A careful family history must be taken followed by a thorough clinical examination (Table 11).

**Table 10: Findings in a newborn suggesting the possibility of DSD (adapted from the American Academy of Pediatrics)**

<b>Apparent male</b>
Severe hypospadias associated with bifid scrotum
Undescended testis/testes with hypospadias
Bilateral non-palpable testes in a full-term apparently male infant
<b>Apparent female</b>
Clitoral hypertrophy of any degree, non-palpable gonads
Vulva with single opening
Indeterminate
Ambiguous genitalia

**Table 11: Diagnostic work-up of neonates with disorders of sex development**

<b>History (family, maternal, neonatal)</b>
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
<b>Physical examination</b>
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
Karyotype
Ultrasound
Genitogram
hCG stimulation test
Androgen-binding studies
Endoscopy

*ACTH = adrenocorticotrophic hormone; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; LH = luteinising hormone; TST = testosterone.*

#### 3.16.2.1.2 Choice of laboratory investigations

The following laboratory investigations are mandatory:

- karyotype;
- plasma 17-hydroxyprogesterone assay;
- plasma electrolytes;
- US to evaluate the presence of Müllerian duct structures.

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

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

#### 3.16.2.2 Gender assignment

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

- age at presentation;
- fertility potential;
- size of the penis;
- presence of a functional vagina;
- endocrine function;
- malignancy potential;
- antenatal testosterone exposure;
- general appearance;
- psychosocial well-being and a stable gender identity;
- sociocultural aspects;
- parental opinions.

Each patient presenting with DSD should be assigned a gender as quickly as a thorough diagnostic evaluation permits. Minimal time needed is 48 hours. During this period any referral to gender should be avoided, better to address the patient as “the child”, “your child”.

#### 3.16.2.3 Role of the paediatric urologist

The role of the paediatric urologist can be divided into a diagnostic role and a therapeutic role (Table 12). Each of these roles will be discussed briefly.

**Table 12: Role of the paediatric urologist**

Diagnostic role
<ul style="list-style-type: none"> <li>• Clinical examination</li> <li>• Ultrasound</li> <li>• Genitography</li> <li>• Cystoscopy</li> <li>• Diagnostic laparoscopy</li> </ul>

### Therapeutic role

- Masculinising surgery
- Feminising surgery
- Gonadectomy

#### 3.16.2.3.1 Clinical examination

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

Palpable gonad: If it is possible to feel a gonad, it is almost certainly a testis; this clinical finding therefore virtually excludes 46XX DSD.

Medical photography can be useful but requires sensitivity and consent [969].

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

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

#### 3.16.2.3.2 Investigations

Ultrasound can help to describe the palpated gonads or to detect non-palpable gonads. However, the sensitivity and specificity are not high. On US, the Müllerian structures can be evaluated. Is there a vagina? Are there some abdominal gonads? Is there a vaginal or utricular structure visible [970, 971]?

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

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

Laparoscopy is necessary to obtain a final diagnosis on the presence of impalpable gonads and on the presence of Müllerian structures. If indicated, a gonadal biopsy can be performed [972, 973].

### 3.16.3 Management

Referring to the consensus document [957, 958], it is clear that the timing of surgery is much more controversial than it used to be. The rationale for early surgery includes:

- beneficial effects of oestrogen on infant tissue;
- avoiding complications from anatomical anomalies;
- minimising family distress;
- mitigating the risks of stigmatisation and gender-identity confusion [974].

However, adverse outcomes have led to recommendations to delay unnecessary surgery to an age when the patient can give informed consent. Surgery that alters appearance is not urgent. Early surgery should be reserved for those patients with high confluent urogenital tracts, girls with severely masculinised genitalia and boys with undervirilised genitals. Vaginoplasty should be delayed until puberty and milder forms of masculinisation should not be treated surgically. Recently the ESPU and the Societies for Pediatric Urology have taken a position in the debate on surgery for DSD [975].

#### 3.16.3.1 Feminising surgery

Clitororeduction. Reduction of an enlarged clitoris should be done with preservation of the neurovascular bundle. Clitoral surgery has been reported to have an adverse outcome on sexual function and should therefore be limited to severely enlarged clitorises [976, 977]. Informed parental consent should be obtained. Although some techniques that conserve erectile tissue have been described, the long-term outcome is unknown [978].

*Separation of the vagina and the urethra* is preserved for high confluence anomalies. Many techniques for urogenital sinus repair have been described, but their outcome has not been evaluated prospectively [979, 980].

*Vaginoplasty* should be performed during the teenage years. Every technique (self-dilatation, skin or bowel substitution) has its specific advantages and disadvantages [981]. All carry a potential for scarring that would require further surgery before sexual function was possible.

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

### 3.16.3.2 Masculinising surgery

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

*Hypospadias surgery:* See section on hypospadias (Chapter 3.5).

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

*Orchiopexy:* See section on orchiopexy (Chapter 3.2).

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

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

*Gonadectomy.* Germ cell malignancy only occurs in patients with DSD who have Y-chromosomal material. The highest risk is seen in patients with gonadal dysgenesis and in patients with partial androgen insensitivity with intra-abdominal gonads (LE: 2). Intra-abdominal gonads of high-risk patients should be removed at the time of diagnosis [982].

### 3.16.4 Summary of evidence and recommendations for the management of disorders of sex development

Summary of evidence	LE
Timing of surgery will be dependent on the severity of the condition and on the assigned sex.	4
In boys the surgical correction will mainly consist of hypospadias repair and orchiopexy, so the timing will follow the recommendations for hypospadias repair and orchiopexy (from six months onwards and before two years of age).	2

Recommendations	Strength rating
Treat disorders of sex development within a multidisciplinary team.	Strong
Refer children to experienced centres where neonatology, paediatric endocrinology, paediatric urology, child psychology and transition to adult care are guaranteed.	Strong
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

## 3.17 Posterior urethral valves

### 3.17.1 Epidemiology, aetiology and pathophysiology

Posterior urethral valves (PUV) are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period. Despite optimal treatment, PUV in children may result in renal insufficiency in nearly one-third of cases [983, 984]. Posterior urethral valves are found in 1 in 1,250 in a population undergoing foetal US screening [684]. An incidence of PUV of 1 in 5,000-12,500 live-births has been estimated [985]. In one report, up to 46% of fetuses with a PUV diagnosis were terminated, indicating a possible decrease in incidence [986].

### 3.17.2 **Classification systems**

#### 3.17.2.1 *Urethral valve*

Despite recent attempts to introduce new classification terms, such as 'congenital obstructive posterior urethral membrane' (COPUM) [987], the original classification by Hugh Hampton Young remains the most commonly used [988].

Hugh Hampton Young described three categories: type I, type II and type III. However, today, only type I and type III are found to be obstructive. As type II seems to be more like a fold and not obstructive, it is no longer referred to as a valve. Hampton Young's descriptions of type I and 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 bulbo-membranous junction. These processes are continued as thin membranous sheets, direct upward and forward which may be attached to the urethra throughout its entire circumference. It is generally supposed that the valves have complete fusion anteriorly, leaving only an open channel at the posterior urethral wall. Yet, the fusion of the valves anteriorly may not be complete in all cases, and at this point a slight separation of the folds exists' [988].

*Type III*. 'There is a third type which has been found at different levels of the posterior urethra and which apparently bears no such relation to the verumontanum. This obstruction was attached to the entire circumference of the urethra, with a small opening in the centre [988]. The transverse membrane described has been attributed to incomplete dissolution from the urogenital portion of the cloacal membrane [989]. The embryology of the urethral valves is poorly understood. The membrane may be an abnormal insertion of the mesonephric ducts into the foetal cloaca [990].

### 3.17.3 **Diagnostic evaluation**

An obstruction above the level of the urethra affects the whole 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 occasionally has multiple diverticula.
- Nearly all valve patients have dilatation of both 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 reflux, the affected kidney functions poorly in most cases.

During prenatal US screening, bilateral hydronephrosis and a distended bladder are suspicious signs of a urethral valve. A thick-walled bladder seems to be of better prediction of a PUV than a dilated posterior urethra ('keyhole' sign) [991]. In the presence of increased echogenicity of the kidney, dilatation of the urinary tract and oligohydramnion, the diagnosis of a PUV should strongly be considered.

Voiding cystourethrogram confirms a PUV diagnosis. This study is essential whenever there is a question of an infravesical obstruction, as the urethral anatomy is well outlined during voiding. A secondary reflux is observed in at least 50% of patients with PUV [992]. Reflux is consistently associated with renal dysplasia in patients with PUV. It is generally accepted that reflux in the renal units acts as a 'pressure pop-off valve', which would protect the other kidney, leading to a better prognosis [993]. Other types of pop-off mechanism include bladder diverticula and urinary extravasation, with or without urinary ascites [994]. However, in the long-term, a supposed protective effect did not show a significant difference compared to other patients with PUV [995, 996].

Nuclear renography with split renal function is important to assess kidney function (DMSA or MAG3). Creatinine, blood urea nitrogen and electrolytes should be monitored closely during the first few days. A nadir creatinine of 80 µmol/L is correlated with a better prognosis [984]. Initial management includes a multidisciplinary team involving a paediatric nephrologist.

### 3.17.4 **Management**

#### 3.17.4.1 *Antenatal treatment*

About 40-60% of PUV are discovered before birth [997]. The intrauterine obstruction leads to a decreased urine output, which could result in an oligohydramnios. Amniotic fluid is necessary for normal development of the lung and its absence may lead to pulmonary hypoplasia, causing a life-threatening problem. Intrauterine attempts have been made to treat a foetus with PUV.

As renal dysplasia is not reversible, it is important to identify those foetuses with good renal function. A sodium level below 100 mmol/L, a chloride value of < 90mmol/L and an osmolarity below 200 mOsm/L found in three foetal urine samples gained on three different days are associated with a better prognosis [998].

The placing of a vesicoamniotic shunt has a complication rate of 21-59%, dislocation of the shunt occurs in up to 44%, mortality lies between 33% and 43%, and renal insufficiency is above 50% [998-1000].

Although shunting is effective in reversing oligohydramnios, it makes no difference to the outcome and long-term results of patients with PUV [999, 1000]. The PLUTO-trial (randomised study) could not prove a benefit of placing a shunt [1001].

Foetal valve treatment e.g laser ablation has a high complication rate without evidence for the effectiveness of these interventions. Therefore this should be still considered as an experimental intervention [1002, 1003].

#### 3.17.4.2 Postnatal treatment

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

**Valve ablation.** When the medical situation of the neonate has stabilised and the creatinine level decreased, the next step is to remove the intravesical obstruction. In cases where the urethra is too small to safely pass a small foetal cystoscope, a suprapubic diversion is performed until valve ablation can be performed. Small paediatric cystoscopes and resectoscopes are now available either to incise, ablate or to resect the valve at the 4-5, 7-8 or 12 o'clock position, or at all three positions, depending on the surgeon's preference. It is important to avoid extensive electrocoagulation, as the most common complication of this procedure is stricture formation. One recently published study demonstrated a significant lower urethral stricture rate using the cold knife compared to diathermy [1004]. Within the three months following initial treatment, a control VCUG or a re-look cystoscopy should demonstrate the effectiveness of the treatment, depending on the clinical course [1005].

**Vesicostomy.** If the child is too small and/or too ill to undergo endoscopic surgery, a suprapubic diversion is performed to drain the bladder temporarily. If initially a suprapubic tube has been inserted, this can be left in place for six to twelve weeks. Otherwise, a cutaneous vesicostomy provides an improvement or stabilisation of the UUT in over 90% of cases [1006]. Although there has been concern that a vesicostomy could decrease bladder compliance or capacity, so far there are no valid data to support these expectations [1007, 1008].

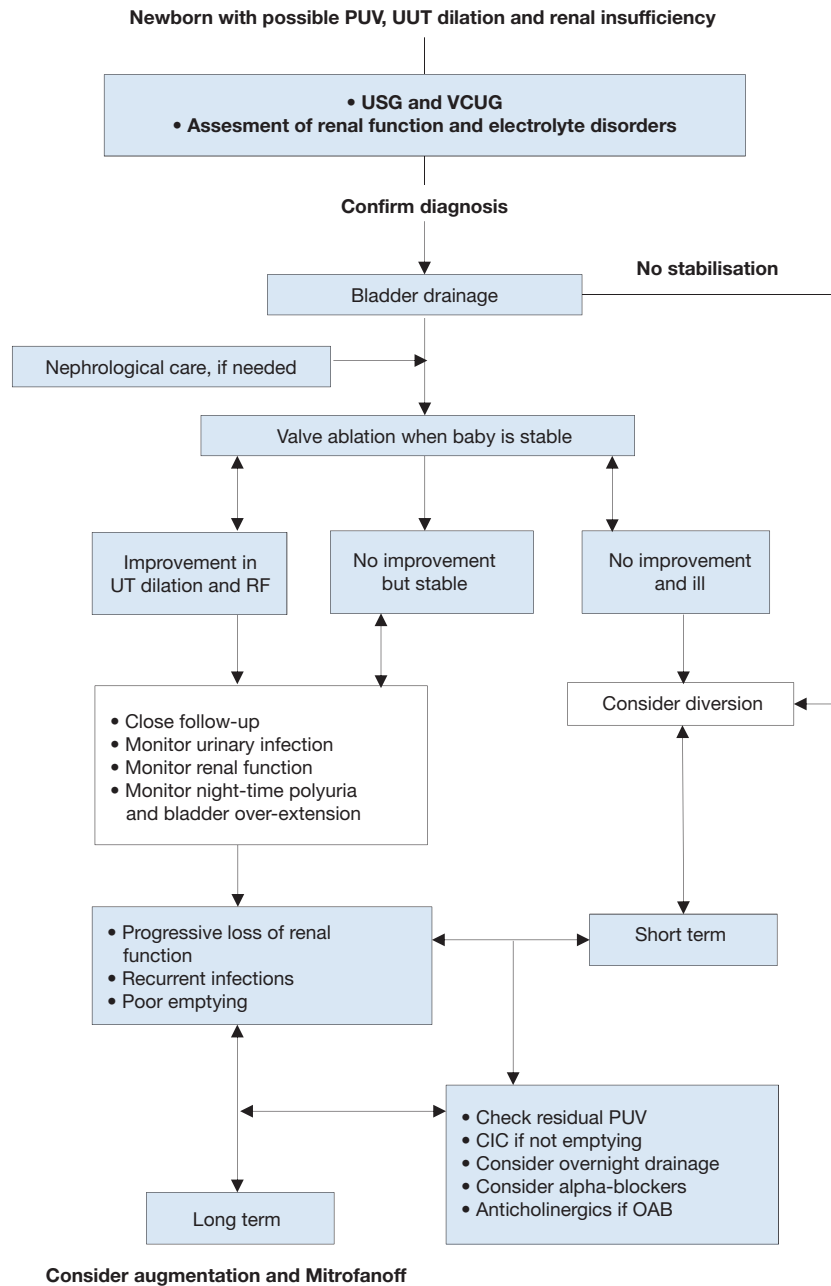
**High diversion.** If bladder drainage is insufficient to drain the UUT, high urinary diversion should be considered. Diversion may be suitable if there are recurrent infections of the upper tract, no improvement in renal function and/or an increase in upper tract dilatation, despite adequate bladder drainage. The choice of urinary diversion depends on the surgeon's preference for high loop ureterostomy, ring ureterostomy, end ureterostomy or pyelostomy, with each technique having advantages and disadvantages [1009-1011]. Reconstructive surgery should be delayed until the UUT has improved as much as can be expected.

Reflux is very common in PUV patients (up to 72%) and it is described bilaterally in up to 32% [1012]. During the first months of life, antibiotic prophylaxis may be given especially in those with high-grade reflux [765] and in those with a phimosis, circumcision can be discussed in order to reduce the risk of UTIs [1013]. However, there are no randomised studies to support this for patients with PUV. High-grade reflux is associated with a poor functioning kidney and is considered a poor prognostic factor [983, 1014]. However, early removal of the renal unit seems to be unnecessary, as long as it causes no problems. It may be necessary to augment the bladder and in this case the ureter may be used [1015].

#### 3.17.5 Follow-up

Life-long monitoring of these patients is mandatory, as bladder dysfunction ('valve bladder') is not uncommon and the delay in day- and night-time continence is a major problem [984, 992, 1016]. Poor bladder sensation and compliance, detrusor instability and polyuria (especially at night) and their combination are responsible for bladder dysfunction. In those with bladder instability, anticholinergic therapy can improve bladder function. However, with a low risk of reversible myogenic failure (3/37 patients in one study) [1017, 1018]. In patients with poor bladder emptying,  $\alpha$ -blocker can be used to reduce the PVR urine, as demonstrated in one study with 42 patients using terazosin (mean PVR) was reduced from 16 to 2 mL [1019] and in another study tamsulosin was effective [1020]. Between 10% and 47% of patients may develop end-stage renal failure [983, 984]. High creatinine nadir and severe bladder dysfunction are risk factors for renal replacement therapy [1021]. Renal transplantation in these patients can be performed safely and effectively [1022, 1023]. Deterioration of the graft function is mainly related to LUTD [1022]. An assessment and treatment algorithm is provided in Figure 10.

Figure 10: 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.

### 3.17.6 Summary

Posterior urethral valves are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period and despite optimal treatment result in renal insufficiency in nearly one-third of cases. Bilateral hydroureteronephrosis and a distended bladder are suspicious signs of a PUV in neonates. A VCUG confirms a PUV diagnosis. Nuclear renography with split renal function is important to assess kidney function and serum creatinine nadir above 80 µmol/L is correlated with a poor prognosis.

Postnatal treatment includes bladder drainage either transurethral or suprapubic and if the child is stable enough, endoscopic incision of the valve is performed. If a child is too small and/or too ill to undergo endoscopic surgery, a vesicostomy is an option for bladder drainage. If bladder drainage is insufficient to drain the UUT, high urinary diversion should be considered.

In all patients life-long monitoring is mandatory, as bladder dysfunction is quite common and may cause progressive upper tract deterioration, if not managed properly. In the long-term between 10% and 47% of patients may develop end-stage renal failure. Renal transplantation in these patients can be performed safely and effectively.

### 3.17.7 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 found during the neonatal period.	1b
Despite optimal treatment nearly one-third of the patients end up in renal insufficiency.	2b
Bilateral hydronephrosis and a distended bladder are suspicious signs on US; a VCUG confirms the diagnosis.	2b
Serum creatinine nadir above 80 µmol/L is correlated with a poor prognosis.	2a
In the long-term between 10% and 47% of patients develop end-stage renal failure due to primary dysplasia and/or further deterioration because of bladder dysfunction. Renal transplantation in these patients is safe and effective, if the bladderfunction is normalised.	2a

Recommendations	LE	Strength rating
Diagnose posterior urethral valves (PUV) initially by ultrasound but a voiding cystourethrogram (VCUG) is required to confirm the diagnosis.	3	Strong
Assess split renal function by dimercaptosuccinic acid scan or mercaptoacetyltriglycine (MAG3) clearance. Use serum creatinine as a prognostic marker.		Strong
Vesico-amniotic shunt antenatally is not recommended to improve renal outcome.	1b	Weak
Offer endoscopic valve ablation after bladder drainage and stabilisation of the child.	3	Strong
Offer suprapubic diversion for bladder drainage if the child is too small for valve ablation.		Strong
Offer a high urinary diversion if bladder drainage is insufficient to drain the upper urinary tract and the child remains unstable.		Strong
Monitor bladder and renal function lifelong, in all patients.	3	Strong

## 3.18 Paediatric urological trauma

Trauma is the leading cause of morbidity and mortality in children and is responsible for more childhood deaths than the total of all other causes [1024]. In about 3% of children seen at paediatric hospital trauma centres, there is significant involvement of the genitourinary tract [1025]. This is caused by either blunt injuries from falls, car accidents, sports injuries, physical assault, and sexual abuse, or penetrating injuries, usually due to falls onto sharp objects or from gunshot or knife wounds.

### 3.18.1 Paediatric renal trauma

#### 3.18.1.1 Epidemiology, aetiology and pathophysiology

In blunt abdominal trauma, the kidney is the most commonly affected organ, accounting for about 10% of all blunt abdominal injuries [1024].

Children are more likely than adults to sustain renal injuries after blunt trauma because of their anatomy. Compared to an adult kidney, a child's kidney is larger in relation to the rest of the body and often retains foetal lobulations, so that blunt trauma is more likely to lead to a local parenchymal disruption. The paediatric kidney is also less well protected than the adult kidney. Children have less peri-renal fat, much weaker abdominal muscles, and a less ossified and therefore much more elastic and compressible thoracic cage [1026].

Blunt renal trauma is usually a result of sudden deceleration of the child's body, particularly due to sport accidents, falls, and contact with blunt objects. Deceleration or crush injuries result in contusion, laceration or avulsion of the less well-protected paediatric renal parenchyma.

#### 3.18.1.2 Classification systems

Renal injuries are classified according to the kidney injury scale of the American Association for the Surgery of Trauma (Table 13) [1027].



**Table 13: Renal injury classified according to the kidney injury scale of the American Association for the Surgery of Trauma [1027]**

Grade	Type of injury	Description
I	Contusion	Non-visible or visible haematuria
	Haematoma	Normal urological studies
II	Haematoma	Non-expanding subcapsular haematoma
	Laceration	Laceration of the cortex of < 1.0 cm
III	Laceration	Laceration > 1.0 cm without rupture of collecting system
IV	Laceration	Through the cortex, medulla and collecting system
	Vascular	Vascular injury
V	Laceration	Completely shattered kidney
	Vascular	Avulsion of the renal hilum

### 3.18.1.3 Diagnostic evaluation

In a child who has sustained blunt abdominal trauma, renal involvement can often be predicted from the history, physical examination and laboratory evaluation. Renal involvement may be associated with abdominal or flank tenderness, lower rib fractures, fractures or vertebral pedicles, trunk contusions and abrasions, and haematuria.

#### 3.18.1.3.1 Haematuria

Haematuria may be a reliable finding. In severe renal injuries, 65% suffer visible haematuria and 33% non-visible, while only 2% have no haematuria at all [1028].

The radiographic evaluation of children with suspected renal trauma remains controversial. Some centres rely on the presence of haematuria to diagnose renal trauma, with a threshold for renal involvement of 50 RBCs/HPF. Although this may be a reliable threshold for significant non-visible in trauma, there have been many reports of significant renal injuries that manifest with little or even no blood in the urine [1029]. It is therefore compulsory to consider all the clinical aspects involved, 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 needs further imaging studies.

#### 3.18.1.3.2 Blood pressure

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 [1030]. Because blood pressure is an unreliable predictor of renal involvement in children, some centres recommend imaging of the urinary tract in children with any degree of haematuria following significant abdominal trauma.

#### 3.18.1.3.3 Choice of imaging method

Nowadays, CT is the best imaging method for renal involvement in children. Computed tomography scanning is the cornerstone of modern staging of blunt renal injuries especially when it comes to grading the severity of renal trauma.

Computed tomography scanning is quite rapid and usually performed with the injection of contrast media. To detect extravasation, a second series of images is necessary since the initial series usually finishes 60 seconds after injection of the contrast material and may therefore fail to detect urinary extravasation [1031]. In acute trauma, US may be used as a screening tool and for reliably following the course of renal injury. However, US is of limited value in the initial and acute evaluation of trauma. The standard intravenous pyelogram (IVP) is a good alternative imaging method if a CT scan is not available. It is superior to US but not as good as CT scanning for diagnostic purposes.

### 3.18.1.4 Disease management

The modern management of trauma is multidisciplinary, requiring paediatricians, emergency physicians, surgeons, urologists, and other specialties as required.

Non-surgical conservative management with bed rest, fluids and monitoring has become the standard approach for treating blunt renal trauma. Even in high-grade renal injuries, a conservative approach is effective and recommended for stable children. However, this approach requires close clinical observation, serial CT scans, and frequent re-assessment of the patient's overall condition.

Absolute indications for surgery include persistent bleeding into an expanding or unconfined haematoma. Relative indications for surgery are massive urinary extravasation and extensive non-viable renal tissue [1032].

### 3.18.1.5 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 with any level of haematuria, especially when the history reveals a deceleration trauma, direct flank trauma or a fall from a height.	Strong
Use rapid spiral computed tomography scanning for diagnostic and staging purposes.	Strong
Manage most injured kidneys conservatively.	Strong
Offer surgical intervention in case of haemodynamic instability and a Grade V renal injury.	Strong

### 3.18.2 Paediatric ureteral trauma

Injuries to the ureter are rare. The ureter is well protected; the upper part is protected by its close approximation 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 [1033]. 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.

#### 3.18.2.1 Diagnostic evaluation

Since there are no classical clinical symptoms suggestive of ureteral trauma, it is important to carry out a careful diagnostic work-up using different imaging modalities. Unfortunately, initial imaging studies, such as IVP and routine CT scans, are unreliable; a study of eleven disruptions of the ureteropelvic junction found that 72% had a normal or non-diagnostic IVP on initial studies [1033]. Diagnostic accuracy of CT scanning can be improved by performing a delayed CT scan up to ten minutes after injection of the contrast material [1034]. The most sensitive diagnostic test is a retrograde pyelogram.

Quite a few patients present several days after the injury, when the urinoma produces flank and abdominal pain, nausea and fever.

Because the symptoms may often be quite vague, it is important to remain suspicious of a potential undiagnosed urinary injury following significant blunt abdominal trauma in a child.

#### 3.18.2.2 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 [1035].

If endoscopic management is not possible, primary repair of partial lacerations should be followed by internal stenting. The management of complete lacerations, avulsions or crush injuries depends on the amount of ureter lost and its location. If there is an adequate healthy length of ureter, a primary ureteroureterostomy can be performed. If primary re-anastomosis 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 [1036].

### 3.18.2.3 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 an urinoma, either percutaneously or via a nephrostomy tube.	Weak

### 3.18.3 Paediatric bladder injuries

The paediatric bladder is less protected than the adult bladder, and is therefore more susceptible to injuries than the adult bladder, especially when it is 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.
- The fact that there is less pelvic and abdominal fat surrounding the bladder to cushion it in 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 sits 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 [1037].

### 3.18.3.1 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 [1038].

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 a CT scan. The best results can be achieved by 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 [1039].

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;
- ruptures, which are either intraperitoneal or extraperitoneal.

Intraperitoneal bladder ruptures are more common in children because of the bladder's exposed position and the acute increase in pressure during trauma. These cause the bladder to burst at its weakest point, i.e. the dome. Extraperitoneal lesions occur in the lower half of the bladder and are almost always associated with pelvic fractures. A cystogram will show extravasation into the perivesical soft tissue in a typical flame pattern and the contrast material is confined to the pelvis.

### 3.18.3.2 Management

Contusions usually present with varying degrees of haematuria and are treated with catheter drainage alone.

#### 3.18.3.2.1 Intraperitoneal injuries

The accepted management of intraperitoneal bladder ruptures is open surgical exploration and primary repair. Post-operative drainage with a suprapubic tube is mandatory. Recent data suggest that transurethral drainage may be as effective, with fewer complications, resulting in shorter periods of diversion [1040]. Usually, after about seven to ten days, a repeat cystogram is performed to ensure healing is taking place properly.

#### 3.18.3.2.2 Extraperitoneal injuries

Non-operative management with catheter drainage for seven to ten days alone 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 [1041].

### 3.18.3.3 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 extra-peritoneal bladder ruptures conservatively with a transurethral catheter left in place for seven to ten days.	Strong
Do not delay treatment of intra-peritoneal bladder ruptures by surgical exploration and repair as well as post-operative drainage for seven to ten days.	Strong

### 3.18.4 Paediatric urethral injuries

Except for the penile part of the urethra, the paediatric urethra is quite well protected. In addition, its shape and elasticity mean 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 a diagnostic work-up.

#### 3.18.4.1 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 are blood at the meatus, visible haematuria, and 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, 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 by someone else and there is suspected urethral trauma, the catheter should be left in place and should not be removed. Instead, a small infant feeding tube can be placed into the distal urethra along the catheter to allow the injection of contrast material for a diagnostic scan [1042].

#### 3.18.4.2 Disease management

Since many of these patients are unstable, 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 may be placed in the emergency department percutaneously, or even in the operating room, if the patient has to undergo immediate exploration because of other life-threatening injuries.

There are often no associated injuries with a bulbous 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 [1043].

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.
- Avoiding the complications of urinary incontinence and impotence.

Suprapubic drainage and late urethral reconstruction was first attempted because immediate surgical repair had a poor outcome, with significant bleeding and high rates of incontinence (21%) and impotence in up to 56% of cases [1044]. In adults, a study of the success rates of delayed repair reported re-structure rates of 11-30%, continence rates of 90-95% and impotence rates of 62-68% [1045]. However, in children, there is much less experience with delayed repair. The largest paediatric series of delayed repair in 68 boys reported a success rate of 90% [1046]. Another study reported strictures and impotence in 67% of boys, although all the boys were continent [1045].

An alternative to providing initial suprapubic drainage and delayed repair is primary realignment of the urethra via a catheter. The catheter is usually put in place during open cystostomy by passing it from either the bladder neck or meatus and through the injured segment. In a series of fourteen children undergoing this procedure, this resulted in a stricture rate of 29% and incontinence in 7% of patients [1047].

#### 3.18.4.3 Recommendations for the diagnosis and management of paediatric trauma

Recommendations	Strength rating
Assess the urethra by retrograde urethrogram in case of suspected urethral trauma.	Strong
Perform a rectal examination to determine the position of the prostate.	Strong
Manage bulbous urethral injuries conservatively with a transurethral catheter.	Strong
Manage posterior urethral disruption by either: <ul style="list-style-type: none"> <li>• primary reconstruction;</li> <li>• primary drainage with a suprapubic catheter alone and delayed repair;</li> <li>• primary re-alignment with a transurethral catheter.</li> </ul>	Weak

### 3.19 Post-operative fluid management

#### 3.19.1 Epidemiology, aetiology and pathophysiology

Compared to adults, children have a different total body fluid distribution, renal physiology and electrolyte requirements, as well as weaker cardiovascular compensation mechanisms [1048]. As children are developing, they have a high metabolic rate and lower fat and nutrient stores, which means they are more susceptible to metabolic disturbances caused by surgical stress [1049]. The metabolic response to anaesthesia and surgery in infants and children is related to the severity of the operation [1050].

### 3.19.2 **Disease management**

#### 3.19.2.1 *Pre-operative fasting*

Pre-operative fasting has been advocated for elective surgery to avoid the complications associated with pulmonary aspiration during induction of anaesthesia. Table 14 gives the current guidelines for pre-operative fasting for elective surgery [1051, 1052].

**Table 14: Pre-operative fasting times for elective surgery**

Ingested material	Minimum fasting period (hours)
Clear liquids	2
Breast milk	4
Infant formula	4 (< 3 months old) to 6 (> 3 months old)
Non-human milk	6
Light meal	6

Although hypoglycaemia is an important issue in children, research has shown that hypoglycaemia is uncommon if children are still fed up to four hours before the induction of anaesthesia [1053]. Newborns often have low glycogen stores and impaired gluconeogenesis, both of which can be helped by limiting the period of pre-operative starvation and feeding with glucose-containing solutions. It is important to monitor blood glucose and to adjust the glucose supply continuously in neonates and children who are small for their age, as this helps to prevent excessive fluctuation in blood glucose levels [1054].

#### 3.19.2.2 *Maintenance therapy and intra-operative fluid therapy*

Generally, the anaesthetist is responsible for intra-operative management and the surgeon is responsible for post-operative instructions. The goal of intra-operative 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 fluids for maintenance therapy replace losses from two sources: insensible (evaporation) and urinary loss. They do not replace blood loss or third-space fluid loss into the interstitial space or gut. The main formulae for calculating the daily maintenance requirement for water have not changed in the past 50 years (Table 15) [1055]. Calculations have shown that anaesthetised and non-anaesthetised children have similar fluid requirements [1056].

The combination of maintenance fluid and electrolyte requirements results in a hypotonic electrolyte solution. The usual intravenous maintenance fluid given to children by paediatricians is one-quarter to one-third strength saline [1057].

**Table 15: Hourly and daily fluid requirements according to body weight**

Body weight	Hourly	Daily
< 10 kg	4 mL/kg	100 mL/kg
10-20 kg	40 mL + 2 mL/kg; > 10 kg	1,000 mL + 50 mL/kg; > 10 kg
> 20 kg	60 mL + 1 mL/kg; > 20 kg	1,500 mL+ 20 mL/kg; > 20 kg

The fasting deficit is calculated by multiplying the hourly maintenance fluid requirement by the number of hours of fluid restriction. It is recommended that 50% of the fasting deficit is replaced in the first hour and 25% in the second and third hours [1058]. Berry proposed simplified guidelines for fluid administration according to the child's age and severity of surgical trauma [1059] (Table 16).

**Table 16: Intra-operative fluid management adapted for children fasted for six to eight hours, following the classical recommendation 'nil per oral after midnight'**

Furman, et al. [1058]			
Hour of fluid replacement	Maintenance fluid	Fasting deficit replacement	Persistent losses
First hour	As Table 15	50%	Third space + blood loss replacement
Second hour		25%	
Third hour		25%	
Berry [1059]			
First hour	< 3 years: 25 mL/kg > 4 years: 15 mL/kg		Blood replacement 1:1 with blood or colloid <b>or</b> 3:1 with crystalloids
All other hours	Maintenance volume = 4 mL/kg/h Maintenance + mild trauma = 6 mL/kg/h Maintenance + moderate trauma = 8 mL/kg/h Maintenance + severe trauma = 10 mL/kg/h		Blood replacement 1:1 with blood or colloid <b>or</b> 3:1 with crystalloids

\* Reduce the amount of fluid given during the first hour if children are fasting for a shorter period of time, or if the child was already being given intravenous fluid prior to surgery.

Five percent dextrose with one-quarter to half-normal saline is often used as a maintenance fluid, while balanced salt solution or normal saline is used as replacement fluid. Blood losses are replaced with a 1:1 ratio of blood or colloid or a 3:1 ratio of crystalloid. However, the administration of a large volume of normal saline can cause dilutional acidosis or hyperchloremic acidosis, while a large volume of balanced salt solution, such as lactated Ringer's solution, can decrease serum osmolality, which is not beneficial in patients with decreased intracranial compliance. If appropriate, albumin, plasma, synthetic colloids, and blood should be administered [1054].

Third-space losses may vary from 1 mL/kg/h for a minor surgical procedure to 15-20 mL/kg/h for major abdominal procedures, or even up to 50 mL/kg/h for surgery of necrotising enterocolitis in premature infants. Third-space losses should be replaced with crystalloids (normal saline or Ringer's lactate) [1052].

Most of the fluids required during surgery are needed to replace fasting deficit or third-space losses, which are mainly extracellular fluids. Hydrating solutions should contain high concentrations of sodium and chloride and low concentrations of bicarbonate, calcium and potassium.

Intra-operative hypoglycaemia is rare in children. In contrast, hyperglycaemia is commonly encountered during anaesthesia and surgery. The replacement fluid should be free of dextrose or should not have > 1% dextrose. Current recommendations include the use of low-dextrose-containing solutions for maintenance fluid therapy, except in patients who are at high risk of hypoglycaemia [1048, 1057]. Intra-operative administration of glucose-free isotonic hydrating solutions should be the routine practice for most procedures in children over four to five years of age. In infants and young children, 5% dextrose solutions should be avoided, but it is appropriate to use 1% or 2% dextrose in lactated Ringer's solution [1052].

### 3.19.2.3 Post-operative fluid management

During the post-operative period, the fundamental principle is to monitor gastrointestinal function and to continue oral or enteral nutrition as much as possible [1049], while remembering that withholding oral fluids post-operatively from children undergoing day surgery helps prevent vomiting [1060]. In minor surgical procedures, intra-operative administration of large volumes of crystalloids is associated with a reduced incidence of post-operative nausea and vomiting after anaesthesia in both paediatric and adult patients [1061]. Berry's fluid replacement guidelines can be followed, provided the child is given lactated Ringer's solution or polyionique B66, which has an osmolarity similar to plasma [1062].

It is not obligatory to check serum chemistry after uncomplicated surgery in children with normal pre-operative 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. Post-operative findings, such as decreased bowel movements and ileus, may be signs of hypokalemia, which may be corrected with a solution of 20 mmol/L potassium and an infusion rate of not more than 3 mmol/kg/day. The potassium should be given via peripheral venous access if the duration of infusion is not expected to exceed five days, or via central venous access when long-term parenteral nutrition is necessary.

The goals of fluid therapy are to provide basic metabolic requirements and to compensate for

gastrointestinal and additional losses. If hypovolemia is present, it should be treated rapidly. Hyponatremia is the most frequent electrolyte disorder in the post-operative period [1062, 1063]. This means that hypotonic fluid should not be routinely administered to hospitalised children because they have several stimuli for producing arginine vasopressin and are therefore at high risk for developing hyponatremia [1052, 1062, 1064-1067]. The preferred fluids for maintenance therapy are 0.45% saline with dextrose or isotonic fluids, in the absence of a specific indication for 0.25% saline. It is also advisable to administer isotonic fluids intra-operatively and also immediately post-operatively, albeit at two-thirds of the calculated maintenance rate in the recovery room. Fluid composition should balance high sodium requirements, energy requirements and solution osmolarity. The extra losses from gastric or chest tubes should be replaced with lactated Ringer's solution. Fluid that has been given to dilute medications must also be taken into account [1052].

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. 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.

#### 3.19.2.4 *Post-operative fasting*

It has been reported that fasting reduces the risk of vomiting by up to 50% [1060, 1068, 1069]. However, a study found that if children were freely allowed to drink and eat when they felt ready or requested it, the incidence of vomiting did not increase and the children felt happier and were significantly less bothered by pain than children who were fasting [1070]. The mean times until first drink and first eating in the children who were free to eat or drink were 108 and 270 minutes, respectively, which were four hours and three hours earlier than in the fasting group. Previous studies have suggested that gastric motility returns to normal one hour after emergence from anaesthesia in children who have undergone non-abdominal surgery [1071]. The first oral intake in children at one hour after emergence from anaesthesia for minor surgery did not cause an increase in the incidence of vomiting, provided that the fluid ingested was at body temperature [1072]. The Panel therefore recommend encouraging an early intake of fluid in children who have undergone minor or non-abdominal urological surgery.

### 3.19.3 **Summary of evidence and recommendations for the management of post-operative fluidmanagement**

Summary of evidence	LE
Children are not simply smaller physiological versions of adults. They have their own unique metabolic features, which must be considered during surgery.	2

Recommendations	Strength rating
Ensure that shorter pre-operative fasting periods apply for elective surgeries (up to four hours).	Strong
Use fluids with lower dextrose concentrations since hyperglycaemia is common in children, compared to intra-operative hypoglycaemia (which is very rare).	Strong
Do not routinely use hypotonic fluid in hospitalised children because they are at high risk of developing hyponatraemia.	Strong
Assess the baseline and daily levels of serum electrolytes, glucose, urea and/or creatinine in every child who receives intravenous fluids, especially in intestinal surgery (e.g. ileal augmentation), regardless of the type of solution chosen since there is an increased risk of electrolyte abnormalities in children undergoing such surgery.	Strong
Start early oral fluid intake in patients scheduled for minor surgical procedures.	Strong

## 3.20 **Post-operative pain management: general information**

### 3.20.1 *Epidemiology, aetiology and pathophysiology*

The provision of adequate pain control requires proper pain evaluation, accurate choice of drug and route of administration, and consideration of age, physical condition and type of surgery and anaesthesia [1073]. However, there is still no standardised algorithm for management of post-operative pain in children [1074]. There is an urgent need for a post-operative pain management protocol in children, particularly for guidance on the frequency of pain assessment, use of parenteral opioids, introduction of regional anaesthesia, and the application of rescue analgesics [1075].

Traditional medical beliefs that neonates are incapable of experiencing pain have now been abandoned following recent and better understanding of how the pain system matures in humans, better pain

assessment methods and a knowledge of the clinical consequences of pain in neonates [1076-1080]. Many studies have indicated that deficient or insufficient analgesia may be the cause of future behavioural and somatic sequelae [1081-1084]. Our current understanding of pain management in children depends fully on the belief that all children, irrespective of age, deserve adequate treatment.

### 3.20.2 **Diagnostic evaluation**

Assessment of pain is the first step in pain management. Validated pain assessment tools are needed for this purpose and it is important to select the appropriate pain assessment technique. Several pain assessment tools have been developed according to the child's age, cultural background, mental status, communication skills and physiological reactions [1085, 1086].

One of the most important topics in paediatric pain management is informing and involving the child and caregivers during this process. Caregivers and patients can manage post-operative pain at home or in hospital if provided with the correct information. Caregivers and patients, if they are old enough, can actively take part in pain management in patient-family-controlled analgesia applications [1087-1092].

### 3.20.3 **Disease management**

#### 3.20.3.1 *Drugs and route of administration*

Pre-emptive analgesia is an important concept that aims to induce the suppression of pain before neural hypersensitisation occurs [1093]. Local anaesthetics or non-steroidal analgesics are given intra-operatively to delay post-operative pain and to decrease post-operative analgesic consumption. Analgesics must be titrated until an appropriate response is achieved. Opioids can be administered to children by the oral, mucosal, transdermal, subcutaneous, intramuscular or intravenous routes [1092]. The combination of opioids with nonsteroidal anti-inflammatory drugs (NSAIDs) or local anaesthetics (balanced or multimodal analgesia) can be used to increase the quality of analgesia and decrease undesired effects related to opioids [1094]. The same combination of local anaesthetics, opioids, and non-opioid drugs used in adults can also be used in children taking into account their age, body weight and individual medical status.

The World Health Organization's 'pain ladder' is a useful tool for the pain management strategy [1095]. A three-level strategy seems practical for clinical use. Post-operative management should be based on sufficient intra-operative pre-emptive analgesia with regional or caudal blockade followed by balanced analgesia.

Paracetamol and NSAIDs are the drugs of choice at the first level. As they become insufficient to prevent pain, weak and strong opioids are added to oral drugs to achieve balanced analgesia. Every institute must build their own strategy for post-operative analgesia. A proposed strategy for post-operative analgesia may be as follows:

1. Intra-operative regional or caudal block.
2. Paracetamol + NSAID.
3. Paracetamol + NSAID + weak opioid (e.g. tramadol or codeine).
4. Paracetamol + NSAID + strong opioid (e.g. morphine, fentanyl, oxycodone or pethidine).

#### 3.20.3.2 *Circumcision*

Circumcision without anaesthesia, irrespective of age, is not recommended. Circumcision requires proper pain management [1096]. Despite this, adequate pain management is still below expectation [1097]. Potential analgesic interventions during circumcision include the use of a dorsal penile nerve block (DPNB) or ring block, topical anaesthetics (e.g. lidocaine-prilocaine cream, or 4% liposomal lidocaine cream), a less painful clamp (e.g. Mogen clamp), a pacifier, sucrose, and swaddling, preferably in combination [1098-1102].

Although DPNB and topical anaesthetics seem to have a similar post-operative analgesic effect, DPNB is still the most preferred method [1103] (LE: 1a). Ultrasound guidance may improve the results, with an increase in procedural time [1104, 1105]. Caudal blockade methods have similar efficacy compared to DPNB. However, caregivers should be informed about the more frequent incidence of post-operative motor weakness and micturition problems [1106-1111].

##### 3.20.3.2.1 *Penile, inguinal and scrotal surgery*

Caudal block is the most studied method for analgesia following surgery for hypospadias. Several agents with different doses, concentrations and administration techniques have been used with similar outcomes [1112-1126]. Both single and combined use of these agents is effective [1113-1115, 1118, 1123, 1124].

Penile blocks can be used for post-operative analgesia and have similar post-operative analgesic properties as caudal blocks [1127]. Two penile blocks at the beginning and end of surgery seems to provide better pain relief [1128]. Severe bladder spasms caused by the presence of the bladder catheter may sometimes cause more problems than pain and is managed with antimuscarinic medications.



For inguinoscrotal surgery, all anaesthetic methods, such as caudal blocks [418, 1129-1131] nerve block [1132, 1133], wound infiltration or instillation, and irrigation with local anaesthetics [1134-1136] have been shown to have adequate post-operative analgesic properties. Combinations may improve the results [1137].

Table 17: List of several drugs used in post-operative pain management in children [1078, 1081, 1089, 1153-1156]

Name	Route of administration	Dose	Side effects	General remarks	Caution
<b>Non-narcotics</b>					
Acetaminophen	Rectal	40 mg/kg loading, 20 mg/kg/dose 4 times/day	Nephrotoxicity, hepatotoxicity (neonates)	Most common used analgesic Antipyretic effect Opioid-sparing effect Wide safety range	Slow onset time and variable absorption via the rectal route; dividing the vehicle is not recommended. Total dose should not exceed: 100 mg/kg for children; 75 mg/kg for infants; 60 mg/kg for term and preterm neonates > 32 weeks post-conceptual age; and 40 mg/kg for preterm neonates < 32 weeks post-conceptual age
	Oral	15-40 mg/kg, followed by 30 mg/ kg/8 h			
	Intravenous	Propacetamol (prodrug)			
Ibuprofen	Oral, rectal	4-10 mg/kg/dose 3-4 times/day		Better analgesic than paracetamol	Safety not established for infants < 6 months old
Diclofenac	Tablet, syrup, suppository	1-1.5 mg/kg 2-3 times/day	Nephrotoxicity, gastrointestinal disturbances	Better than ibuprofen	> 6 years old
Ketorolac	Oral, IV, IM	0.2-0.5 mg/kg every 6 h (48 h) Total dose < 2 mg/kg/day, maximum 5 days		Opioid-sparing effect	
Ketamine	Oral, rectal, IM, SC, IV, intraspinal	< 2 mg/kg (IM) < 1 mg/kg (IV, epidural)			
Metamizole, dipyrrone	Oral, IM Oral drop	10-15 mg/kg/dose (max 40 mg/ kg total) 10-15 mg/kg 1 drop/kg/dose, up to 4 times/day	Risk of agranulocytosis, not clarified definitely	Very effective antipyretic	Not approved in some countries including USA, Sweden, Japan and Australia
<b>Narcotics</b>					
<b>Opioids</b>					
Tramadol (weak opioid)	Oral, rectal, IV, IM (dose can be repeated 4-6 times/day)	2-3 mg/kg/dose (oral, drop) 1-2 mg/kg/dose (oral, tablet) 1.5-3 mg/kg/dose (rectal) 0.75-2 mg/kg/dose (IM) 2-2.5 mg/kg/dose (IV) 0.1-0.25 mg/kg/h (continuous)	Nausea, vomiting, dyspepsia, constipation, urinary retention, respiratory depression, drowsiness, euphoria Nausea, vomiting, pruritus and rash	Does not inhibit prostaglandin synthesis	An IM injection is not recommended. Slow IV infusion. Be careful in patients taking psychoactive medications and with seizures

Codeine	Oral	1 mg/kg, single dose	Respiratory depression not seen after single dose	Both antitussive and analgesic effect	
Morphine	IM, IV	6-12 months: 0.1 mg/kg, IM 0.05 mg/kg, IV		Most commonly used opioid, but not the most suitable opioid for pain relief in children	IM injection not recommended < 2 months old: be careful
Nalbuphine	IV	< 3 months old: 0.05 mg/kg/dose > 3 months old: 0.05-0.10 mg/kg/dose (4-6 times/day)			
Piritramide	IV	0.05-0.10 mg/kg/dose (4-6 times/day)			
Dextromethorphan	Oral, syrup	1 mg/kg			
Pethidine/meperidine	IM, IV	1.5-2 mg/kg IM as premedicant 1 mg/kg IV as analgesic	No advantage over morphine		
Fentanyl	IV	1-2 µg/kg			
Buprenorphine	IV	3-5 mg/kg			
Pentazocine	IV, IM	1 mg/kg IM 0.5-0.75 mg/kg IV	In small infants, observe respiration after IV administration		
<b>Regional (local) anaesthetics</b>					
Bupivacaine		Maximum single bolus dose: 2.5-3.0 mg/kg Maximum infusion: 0.4-0.5 mg/kg/h (10-20 mg/kg/day) in older infants and children; 0.2-0.25 mg/kg/h (5-6 mg/kg/day) in neonates	Cardiotoxicity, convulsion		
Levobupivacaine	IV, IM	0.2-0.25% 1-2.5 mg/kg for single-shot epidural 0.2-0.4 mg/kg/h for IV continuous administration	Less toxic than bupivacaine		
Ropivacaine	IV, IM	0.2-0.25% 1-2.5 mg/kg for single-shot epidural 0.2-0.4 mg/kg/h for IV continuous administration	Less toxic than levobupivacaine		

### 3.20.3.3 Bladder and kidney surgery

Continuous epidural infusion of local anaesthetics [1138-1140], as well as systemic (intravenous) application of analgesics [1141], has been shown to be effective. Ketorolac is an effective agent that is underused. It decreases the frequency and severity of bladder spasms and the length of post-operative hospital stay and costs [1130, 1142-1145].

Open kidney surgery is particularly painful because all three muscle layers are cut during conventional loin incision. A dorsal lumbotomy incision may be a good alternative because of the shorter post-operative hospital stay and earlier return to oral intake and unrestricted daily activity [1146].

Caudal blocks plus systemic analgesics [1147], and continuous epidural analgesia, are effective in terms of decreased post-operative morphine requirement after renal surgery [1148, 1149]. However, when there is a relative contraindication to line insertion, a less experienced anaesthetist is available, or caregivers prefer it [1150], non-invasive regimens composed of intra-operative and post-operative analgesics may be the choice. Particularly in this group of patients, stepwise analgesia protocols can be developed [1151]. For laparoscopic approaches, intra-peritoneal spraying of local anaesthetic before incision of the perirenal fascia may be beneficial [1152].

**Table 18: A simple pain management strategy for paediatric urological surgery**

Intensity of surgery	First step	Second step	Third step
Mild (inguinal, scrotal, penile)	Paracetamol and wound infiltration with local anaesthetics	non-steroidal anti-inflammatory drugs (NSAIDs)	Regional block/weak opioid or IV strong opioid with small increments as rescue analgesia (e.g. nalbuphine, fentanyl, meperidine, morphine)
Moderate (lower abdominal)			Peripheral nerve block (single shot or continuous infusion)/opioid injection (intravenous patient-controlled analgesia (IV PCA))
Severe (upper abdominal or lumbotomy)			Epidural local/major peripheral nerve/plexus block/opioid injection (IV PCA)

### 3.20.4 Summary of evidence and recommendations for the management of post-operative pain

Summary of evidence	LE
Neonates experience pain.	3
Pain may cause behavioural and somatic sequelae.	3
Every institute must develop their own well-structured strategy for post-operative analgesia.	4

Recommendations	Strength rating
Prevent/treat pain in children of all ages.	Strong
Evaluate pain using age-compatible assessment tools.	Strong
Inform patients and caregivers accurately.	Strong
Use pre-emptive and balanced analgesia in order to decrease the side effects of opioids.	Strong

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## 5. 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 publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/>. This Guidelines document was developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

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