EAU Guidelines on

Paediatric Urology

S. Tekgül (Chair), H.S. Dogan, R. Kocvara,
J.M. Nijman (Vice-chair), C. Radmayr, R. Stein
Guidelines Associates: M.S. Silay,
S. Undre, J. Quaedackers

espu

European Society for Paediatric Urology

European Association of Urology

TABLE OF CONTENTS PAGE

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 addresses 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 distinct 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 approach is available.

Over time, paediatric urology has informally 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 care-givers 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 Uroweb: http://uroweb.org/guideline/paediatric-urology/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, in print and in a number of versions for mobile 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. This 2017 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 2017 publication:

- Section 3.4 - Acute scrotum in children: The literature has been updated resulting in minor revisions to the text;
- Section 3.5 - Hypospadias: Both the literature and the text have been revised extensively;
- Section 3.6 - Congenital penile curvature: Both the literature and the text have been revised extensively;
- 3.12 - Dilatation of the upper urinary tract (UUT) (UPJ and UVJ obstruction). A new section presenting the results of a systematic review interrogating the role of antibiotic prophylaxis in antenatal hydronephrosis has been included [4];
- Section 3.14 - Urinary stone disease: Both the literature and the text have been revised extensively.

1.5.1 *New and changed recommendations*

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	GR
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	A
Provide photo documentation of the erect penis from different angles as a prerequisite in the pre-operative evaluation.	1b	A
Perform surgery after weighing aesthetic as well as functional implications of the curvature.	2b	B
At the beginning as well as at the end of surgery perform artificial erection tests.	2a	A

3.5.6 *Summary of evidence and recommendations for the management of hypospadias*

Summary of evidence	LE
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 rate (between 28 and 68%) can occur in two-stage repairs.	3

Recommendations	GR
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.	B
Ensure long-term follow-up to detect urethral stricture, voiding dysfunctions and recurrent penile curvature.	A
Use validated objective scoring systems to assist in evaluating the functional and cosmetic outcome.	A

3.12.5 *Summary of evidence and recommendations for the management of ureteropelvic junction (UPJ)-, UVJ-obstruction*

Summary of evidence	LE
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

Recommendation	LE	GR
Offer continuous antibiotic prophylaxis to the subgroup of children with antenatal hydronephrosis who are at high risk of developing urinary tract infection (uncircumcised infants (LE: 1a), children diagnosed with hydroureteronephrosis (LE: 1b) and high-grade hydronephrosis (LE: 2).	2	A

2. METHODS

These Guidelines were compiled based on current literature following a structured review using MEDLINE. Application of a structured analysis of the literature was not possible in many conditions due to a lack of well-designed studies. 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.

Recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: http://uroweb.org/guidelines/.
A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.1 Peer review

The following section was peer-reviewed prior to publication:

- Chapter 3.2 - Undescended testes.

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

2.2 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 varicocoele intervention in children?

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 [6].

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) [6]. Balanitis xerotica obliterans, also termed lichen sclerosis, has been recently found 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. Chronic inflammation was the most common finding [7] (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 [8]. 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 fraenulum 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. 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% [9-12] (LE: 1b). A recurrence rate of up to 17% can be expected [13]. This treatment has no side effects and the mean bloodspot

cortisol levels are not significantly different from an untreated group of patients [14] (LE: 1b). The hypothalamic pituitary-adrenal axis was not influenced by local corticoid treatment [15]. Agglutination of the foreskin does not respond to steroid treatment [11] (LE: 2).

Operative treatment of phimosis in children is dependent on the parents' preferences and can be plastic or radical circumcision after completion of the second year of life. Alternatively, the Shang Ring may be used especially in developing countries [16]. Plastic circumcision has the objective of achieving a wide foreskin circumference with full retractability, while the foreskin is preserved (dorsal incision, partial circumcision). However, this procedure carries the potential for recurrence of the phimosis [17]. In the same session, adhesions are released and an associated fraenulum 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 [18-21] (LE: 2b). Male circumcision significantly reduces the bacterial colonisation of the glans penis with regard to both non-uropathogenic and uropathogenic bacteria [22] (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 [23]. 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 [24, 25]. Circumcision can be performed in children with coagulopathy with 1-5% suffering complications (bleeding), if haemostatic agents or a diathermic knife are used [26, 27]. Childhood circumcision has an appreciable morbidity and should not be recommended without a medical reason and also taking into account epidemiological and social aspects [28-32] (LE: 1b).

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 [33, 34] (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 parents' 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**	**GR**
Treat primary phimosis conservatively with a corticoid ointment or cream. Circumcision will also solve the problem if being considered.	1b	A
Do not delay treatment of primary phimosis in recurrent balanoposthitis and recurrent urinary tract infection (UTI) in patients with urinary tract abnormalities.	2b	A
Circumcision is indicated in secondary phimosis.	2b	A
Do not delay treatment in case of paraphimosis, this is an emergency situation. Perform a dorsal incision of the constrictive ring if manual reposition has failed.	3	B
Routine neonatal circumcision is not recommended to prevent penile carcinoma.	2b	B

3.2 Management of undescended testes

*3.2.1 **Background***

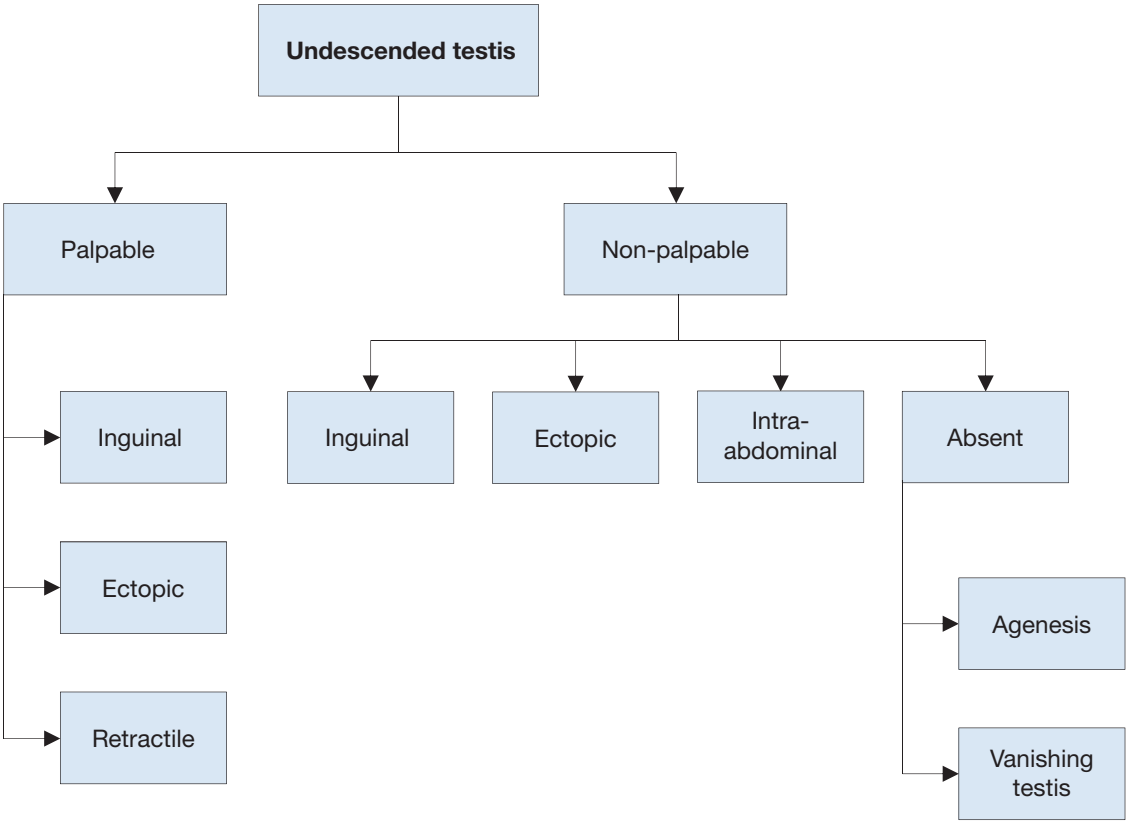
Cryptorchidism or undescended testis is one of the most common congenital malformations of male neonates. Incidence varies and depends on gestational age, affecting 1.0-4.6% of full-term and 1.1-45% of preterm neonates. Following spontaneous descent within the first months of life, nearly 1.0% of all full-term male infants still have undescended testes at one year of age [35]. This congenital malformation may affect both sides in up to 30% of cases [36]. 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 [37].

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 [38]. 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 [39]. 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 [40].

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 [41].

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

Parents 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 [42]. 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 [43]. 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 [44]. Nevertheless, this does not preclude surgical exploration since the sign of compensatory hypertrophy is not specific enough [45].

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 [46].

3.2.3.3 Imaging studies

Imaging studies cannot determine with certainty that a testis is present or not [47]. Ultrasound (US) lacks the diagnostic performance to detect the testis confidently or establish the absence of an intra-abdominal testis [48].

Consequently, the use of different imaging modalities, such as US or magnetic resonance imaging (MRI) [49], 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) [50].

3.2.4 ***Management***

Treatment should be started at the age of six months. After that age, undescended testes rarely descend [51]. 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 [52]. 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 [53].

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 [54, 55].

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 maximum success rate of only 20% [56]. However, it must be taken into account that almost 20% of these descended testes have the risk of re-ascending later [54]. 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 [55]. 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 [57]. The Panel consensus is that endocrine treatment to achieve testicular descent is not recommended (LE: 4).

Human chorionic gonadotropin (hCG)

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 [58]. Similar response rates were achieved with 500 IU once weekly and 1.50 IU three times weekly [59]. 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 [60].

Gonadotropin-releasing hormone (GnRH)

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 [61].

3.2.4.1.2 Medical therapy for fertility potential

Hormonal treatment may improve fertility indices [61, 62] 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 [63]. 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 [64].

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 [65].

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 [66]. The Panel consensus recommends endocrine treatment with GnRH analogues in a dosage described above for boys with bilateral undescended testes to preserve the fertility potential (LE: 4, GR: C).

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 [52]. In addition, early orchidopexy can be followed by partial catch-up testicular growth, which is not the case in delayed surgery [67]. All these findings recommend performing early orchidopexy between the ages of six and twelve months [51].

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 [68].

3.2.4.2.1.1 Inguinal orchidopexy

Inguinal orchidopexy is a widely used technique with a high success rate of up to 92% [69]. 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 [70]. 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 epididimys to the testis can be judged and decribed 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 [71]. With regard to fixation sutures, if required, they should be made between the tunica vaginalis and the dartos musculature [72]. 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 [73].

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 [74]. 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 [75]. 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% [68].

3.2.4.2.2 Non-palpable testes

For non-palpable testes, surgery must clearly determine whether a testis is present or not [76]. 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 [77]. Subsequent removal or orchidolysis and orchidopexy can be carried out using the same approach to achieve the therapeutic aims [78]. Some tend to start with inguinal surgical exploration, with possible laparoscopy during the procedure [79]. 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 [80].

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%) [81].

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 [82]. A peeping testis can be placed down in the scrotum laparoscopically or via an inguinal incision [83]. 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 [84]. Under such circumstances, a Fowler-Stephens orchidopexy may be an option [85] (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 [86]. Due to the nature of these approaches the testis is at risk of hypotrophy or atrophy if the collateral blood supply is insufficient [87]. 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 [88]. 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 [89]. In addition preservation of the gubernaculum may also decrease the chance of testicular atrophy [90].

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 [91].

3.2.4.2.3 Complications of surgical therapy

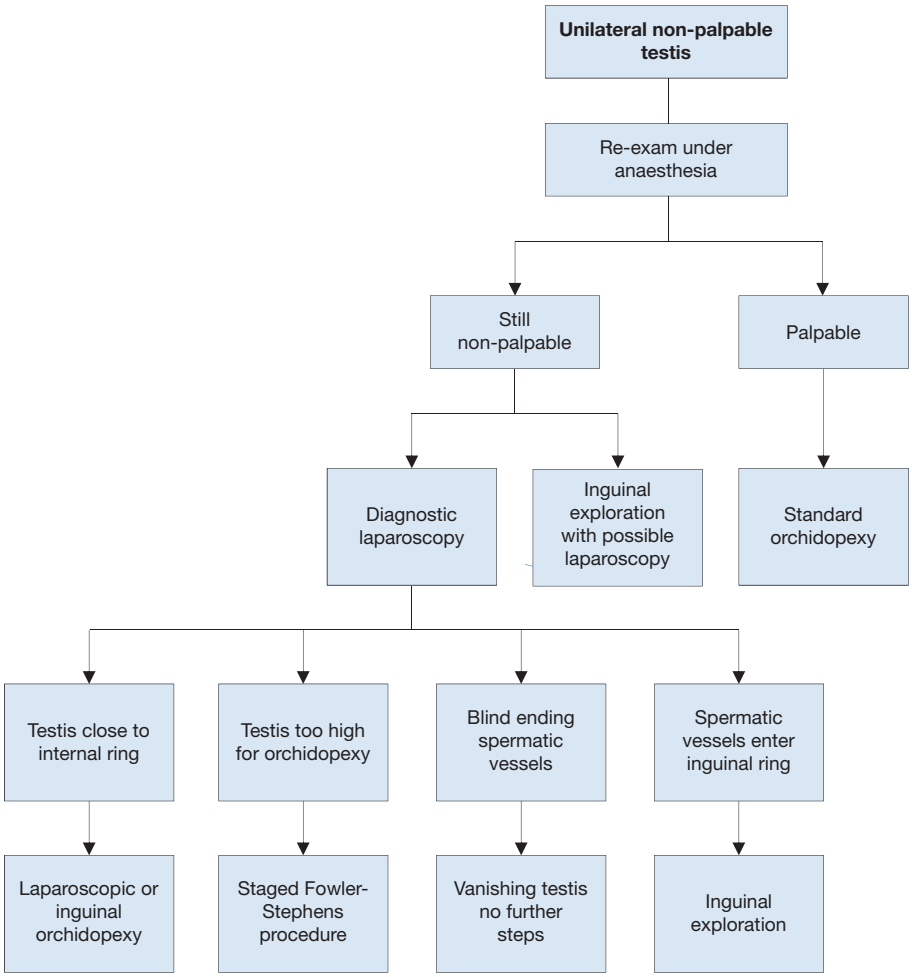
Surgical complications are usually uncommon, with testicular atrophy being the most serious. A systematic review revealed an overall atrophy rate for primary orchidopexy of 1.83%, 28.1% for one-stage Fowler-Stephens procedure, and 8.2% for the two-stage approach [92]. Other rare complications comprise 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% [93].

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 [94] is extensively discussed in the literature and seems to be a result of multiple factors, including germ cell loss, impaired germ cell maturation [95], Leydig cell diminution and testicular fibrosis [96].

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 [97]. The age at which surgical intervention for an undescended testis happens 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 [98]. 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 [99].

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 [96].

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 [52].

*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 [100]. 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 [101].

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 [102].

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

Summary of evidence	**LE**
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**	**GR**
Boys with retractile testes do not need medical or surgical treatment, but ensure close follow-up until puberty.	2a	A
Perform surgical orchidolysis and orchidopexy before the age of twelve months, and by eighteen months at the latest.	2b	B
Evaluate male neonates with bilateral non-palpable testes for possible disorders of sex development (DSD).	1b	A
In case of non-palpable testes and no evidence of DSDs, laparoscopy is recommended because of its excellent sensitivity and specificity in identifying an intra-abdominal testis, as well as the possibility for subsequent treatment in the same session.	1a	A
Do not routinely offer hormonal therapy, either in an adjuvant or neo-adjuvant setting. Patients have to be evaluated on an individual basis.	2a	C
In case of bilateral undescended testes, offer endocrine treatment.	4	C
For an undescended testis in a post-pubertal boy or older, with a normal contralateral testis, discuss removal with the patient/parents because of the theoretical risk of a later malignancy.	3	B

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 [103]. 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 [104]. 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 [105]. If complete obliteration

of the processus vaginalis occurs with patency of midportion, a hydrocele of the cord occurs. Scrotal hydroceles without associated patency of the processus vaginalis are also encountered in newborns [106]. 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 [107, 108]. 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 nontender. 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 [109] (LE: 2). Little risk is taken by initial observation as progression to hernia is rare and does not result in incarceration [109]. Early surgery is indicated if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology [110, 111] (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 [112].

The question of contralateral disease should be addressed by both history and physical examination at the time of initial consultation (LE: 2) [113]. 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 [114]. 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 [103, 108, 110] (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 [108, 110] (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**	**GR**
In the majority of infants, observe hydrocele for twelve months prior to considering surgical treatment.	2a	B
Perform early surgery if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology.	2b	B
Perform a scrotal ultrasound in case of doubt about the character of an intrascrotal mass.	4	C
Do not use sclerosing agents because of the risk for chemical peritonitis.	4	C

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 [115-120]. 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) [121-133]. Trauma can also be a cause of acute scrotum as it can relate to post-traumatic haematomas, testicular contusion, rupture dislocation or torsion [134-139]. 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 [140].

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 [118, 141, 142]. One study predicted the annual incidence of epididymitis around 1.2 per 1,000 children [143]. Perinatal torsion of the testis most often occurs prenatally. Bilateral torsion comprises 11-21% of all perinatal cases [144]. 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 [145, 146].

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%) [117, 118, 142].

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 [142].

An abnormal (horizontal) position of the testis is more frequent in testicular torsion than epididymitis [117]. Looking for absence of the cremasteric reflex is a simple method with 100% sensitivity and 66% specificity for testicular torsion [141, 146] (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 [116, 117, 141, 147]. In many cases, it is not easy to determine the cause of acute scrotum based on history and physical examination alone [115-120, 141, 147].

A positive urine culture is only found in a few patients with epididymitis [119, 141, 147, 148]. 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, and a positive predictive value of 100% and negative predictive value of 97.5% [149-154] (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 [151, 155]. 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 [151]. 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% [151, 156] (LE: 2).

Scintigraphy and, more recently, dynamic contrast-enhanced subtraction MRI of the scrotum also provide a comparable sensitivity and specificity to US [157-160]. 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 [147].

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 [161]. 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 [119, 141, 143].

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 [143, 162]. 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 [163].

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 [164] (LE: 3; GR: C). Doppler US may be used for guidance [165]. 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 [164, 166].

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 [154].

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 [167]. Severe testicular atrophy occurred after torsion for as little as four hours when the turn was > 360°. In cases of incomplete torsion (180-360°), with symptom duration up to twelve hours, no atrophy was observed. However, an absent or severely atrophied testis was found in all cases of torsion > 360° and symptom duration > 24 hours [168].

Early surgical intervention with detorsion (mean torsion time less than thirteen hours) was found to preserve fertility [169]. 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 [167, 168] (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 [170].

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 [171]. Incision of the tunica albuginea with tunica vaginalis graft to prevent or treat compartment syndrome has also been suggested [172].

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 [173-177]. It is good clinical practice to perform fixation also 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 intra-operatively assessed as viable, and should be counseled accordingly [178].

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 [179].

A recent study showed a normal pregnancy rate after unilateral testicular torsion, with no difference between the patients undergoing orchidopexie and those after orchidectomy [180].

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 [167]. 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 [169].

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 [167].

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 [170].

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 and 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**	**GR**
Do not delay intervention since testicular torsion is a paediatric urological emergency.	3	A
In neonates, also explore the contralateral scrotum.	3	C
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	B
Manage torsion of the appendix testis conservatively. Perform surgical exploration in equivocal cases and in patients with persistent pain.	3	B
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	C

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 [181, 182]. 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 increasing in the USA [183, 184].

3.5.2 ***Risk factors***

Risk factors associated with hypospadias are likely to be genetic, placental and/or environmental [181, 182] (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 [182, 185] (LE: 2b).

- An additional family member with hypospadias is found in 7% of families, but this is more predominant in anterior and middle forms [185-188].
- Endocrine disorders can be detected in rare cases.
- Babies with a low birth weight have a higher risk of hypospadias [185-188].

- 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 [187-190] (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 2 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 [191] (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 parent or future patient's psychology, are:

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

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

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 [192] (LE: 4) (Figure 1). 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 [190, 193, 194]. It leads to significant enlargement of the glans and shaft of the penis (LE: 1b).

Pre-operative testosterone administration is most often well tolerated. Transient side effects on child´s behaviour, appearance of pubic hair, 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 [194, 195].

3.5.5.3 Age at surgery

The age at surgery for primary hypospadias repair is usually 6-18 (24) months [192, 196, 197] (LE: 3). Age at surgery is not a risk factor for urethroplasty complication in pre-pubertal tubularised incised plate urethroplasty (TIP) repair [196] (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 [198] (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% [199]. The urethral plate has well vascularised connective tissue and does not cause curvature in most cases [200, 201]. 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°), 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) [202]. 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 [203] (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 [201]. Mobilisation of the corpus spongiosum/urethral plate and the bulbar urethra decreases the need for urethral plate transection [202] (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 treatment of choice in distal and mid-penile hypospadias [204-208]. 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 [209]. This also enables extension of the incision beyond the end of the plate to prevent meatal stenosis [210, 211] (LE 2a).

For distal forms of hypospadias, a range of other techniques is available (e.g. Mathieu, urethral advancement) [212] (LE: 2b). The TIP technique has become an option for proximal hypospadias as well [204-208]. However, urethral plate elevation and urethral mobilisation should not be combined with TIP repair because it results in focal devascularisation of the neourethra with symptomatic stricture development [213] (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 [199]. An onlay preputial graft is an option for single-stage repair [214] (LE: 2b).

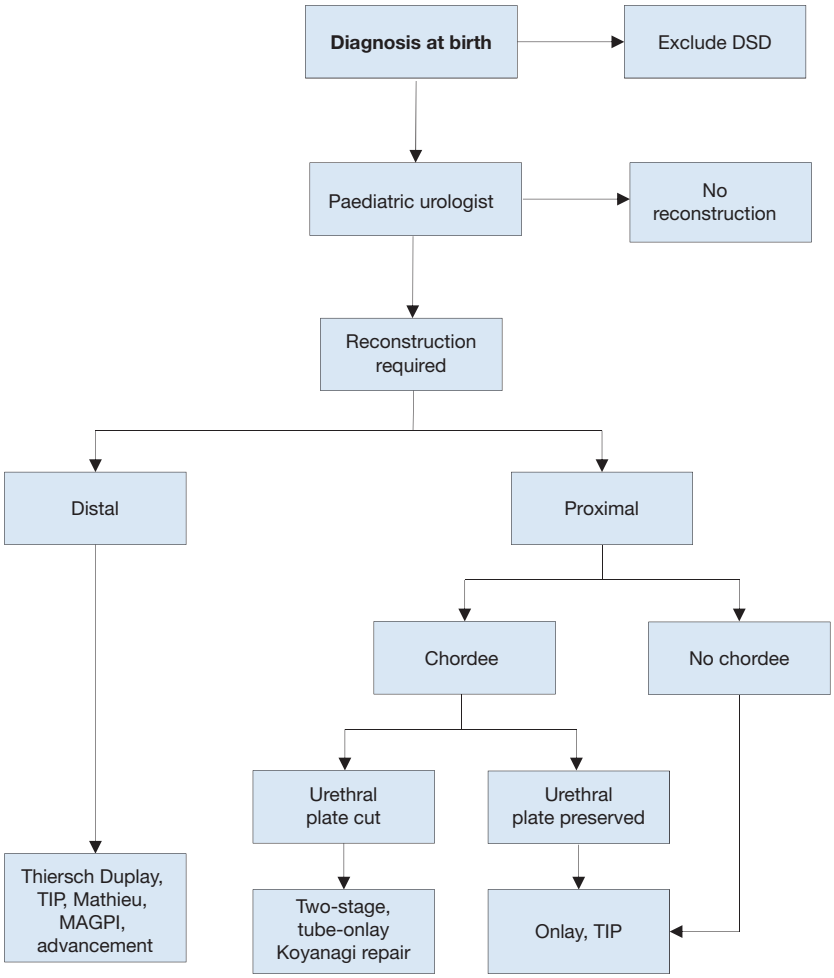
If the continuity of the urethral plate cannot be preserved, single or two-stage repairs are used. For the former, a modification of the tubularised flap (Duckett tube), such as a tube-onlay or an inlay-onlay flap, or onlay

flap on albuginea are used to prevent urethral stricture [215-217] (LE: 3); alternatively the Koyanagi-Hayashi technique is used [218-221]. 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 [211, 217, 222-226].

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 neourethra.

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 [227]. In the TIP repair, the use of a preputial dartos flap reduces the fistula rate [204, 205] (LE: 2b).

3.5.5.8 Urine drainage and wound dressing

Urine is drained transurethrally (eg. dripping stent) or with a suprapubic tube. No drainage after distal hypospadias repair is another option [228, 229]. Circular dressing with slight compression, as well as prophylactic antibiotics during surgery, are established procedures [228] (LE: 4). Post-operative prophylaxis after hypospadias repair is controversial [230, 231] (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 [228, 232]. Low surgeon volume independently increases the risk of fistula, stricture or diverticulum repair [228, 233] (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%) [204-208, 228]. One should expect a predictable outcome with complication rates below 10% in distal hypospadias (fistula, meatal stenosis, dehiscence, recurrent ventral curvature, and haematoma) [233, 234]. A similar incidence of fistula (3.4-3.6%) can be expected after the Mathieu and TIP repairs of distal hypospadias [208, 235, 236].

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 [199]. The complication rate of single-stage Koyanagi and Hayashi modification repairs goes up 61%, according to a comparative study [220, 228]. 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 [235, 237]. A recent long-term study on two-stage flap repair showed a complication rate of 68% [228], another study showed a re-operation rate of 28% [211, 228].

*3.5.6 **Follow-up***

Long-term follow-up is necessary up to adolescence to detect urethral stricture, voiding dysfunctions and recurrent penile curvature. Up to half of complications requiring re-operation present after the first year post-operatively [238] (LE: 2b).

Obstructive flow curve is common after hypospadias repair and while most are not clinically significant, long-term follow-up is required [239-242] (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 [243] (LE: 2a).

Objective scoring systems have been developed in order to evaluate the results of hypospadias surgery (HOSE) [244] (LE: 2b) and cosmetic appearance (HOPE-Hypospadias Objective Penile Evaluation) [245] (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 parents and uninvolved urologists [246] (LE: 2a).

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 [247, 248] (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 PPS, 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 [228, 249].

According to a systematic review of long-term patient satisfaction with cosmetic outcomes [250]:

- 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.

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 rate (between 28 and 68%) can occur in two-stage repairs.	3
Sexual functions are usually well preserved.	2b

Recommendations	GR
At birth, differentiate isolated hypospadias from disorders of sex development which are mostly associated with cryptorchidism or micropenis.	A
Counsel parents on functional indications for surgery, aesthetically feasible operative procedures (psychological, cosmetic indications) and possible complications.	A
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.	B
For distal hypospadias, use 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.	B
Ensure long-term follow-up to detect urethral stricture, voiding dysfunctions and recurrent penile curvature.	A
Use validated objective scoring systems to assist in evaluating the functional and cosmetic outcome.	A

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 [251] because of developmental arrest during embryogenesis [252]. 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 [253]. Most of the cases are ventral deviations (48%), followed by lateral (24%), dorsal (5%), and a combination of ventral and lateral (23%) [254]. Most ventral curvatures are associated with hypospadias due to chordee or ventral dysplasia of cavernous bodies [255]. 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 [256]. 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 [257]. 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 [258]. 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 [259, 260]. Reviews comparing the outcome of Nesbit/modified Nesbit procedures [261] to plication procedures [262] 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 [263]. 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 [264, 265].

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 [266].

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	GR
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	A
Provide photo documentation of the erect penis from different angles as a prerequisite in the preoperative evaluation.	1b	A
Perform surgery after weighing aesthetic as well as functional implications of the curvature.	2b	B
At the beginning as well as at the end of surgery perform artificial erection tests.	2a	A

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 [267-269].

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 varicocelectomy in adolescents [270, 271]. An average proportion of catch-up growth of 76.4% (range: 52.6-93.8%) has been found according to a recent meta-analysis [272] (LE: 2a). However, this may partly be attributable to testicular oedema associated with the division of lymphatic vessels [273] (LE: 2).

In about 20% of adolescents with varicocele, fertility problems will arise [274]. The adverse influence of varicocele increases with time. Improvement in sperm parameters has been demonstrated after adolescent varicocelectomy [275-278] (LE: 1).

3.7.1 Classification systems

Varicocele is classified into 3 grades [279]:

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

3.7.2 *Diagnostic evaluation*

Varicocele is mostly asymptomatic, rarely causing pain. It may be noticed by the patient or parents, or discovered by the paediatrician at a routine visit. The diagnosis depends upon the clinical finding of a collection of dilated and tortuous veins in the upright posture; the veins are more pronounced when the patient performs the Valsalva manoeuvre. 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 [280]. 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 [281] (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 [276, 282].

3.7.3 *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 [283] (LE: 4). The recommended indication criteria for varicocelectomy in children and adolescents are [268]:

- varicocele associated with a small testis;
- additional testicular condition affecting fertility;
- bilateral palpable varicocele;
- pathological sperm quality (in older adolescents);
- symptomatic varicocele [283].

Testicular (left + right) volume loss in comparison with normal testes is a promising indication criterion, once the normal values are available [284]. 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 [285-288].

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 [285, 287]. 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 [273, 285, 286, 289] (LE: 2). The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs, or suprainguinal open or laparoscopic lymphatic-sparing repairs [285, 287, 290, 291]. Intrascrotal application of isosulphan blue was recommended to visualise the lymphatic vessels [292, 293]. 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 [294, 295].

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 [296, 297]. 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 [268, 296, 297] (LE: 2).

3.7.4 *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%; 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	GR
Examine varicocele in the standing position and classify into three grades.	4	A
Use scrotal ultrasound to detect venous reflux without Valsalva manoeuvre in the supine and upright position and to discriminate testicular hypoplasia.		
In pre-pubertal boys and in isolated right varicocele perform standard renal ultrasound to exlude a retroperitonal mass.		
Perform surgery for: • varicocele associated with a small testis (size difference of > 2 mL or 20%); • additional testicular condition affecting fertility; • pathological sperm quality (in older adolescents); • bilateral palpable varicocele; • symptomatic varicocele.	2	B
Use some form of optical magnification (microscopic or laparoscopic magnification) for surgical ligation.	2	B
Use lymphatic-sparing varicocelectomy to prevent hydrocele formation and testicular hypertrophy.	2	A

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 [298-300]. 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 [301-304].

The incidence varies depending on age and sex. One meta-analysis showed 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 [302]. 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 [302-305].

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 [306], however, it is less frequent in community-acquired than in nosocomial UTI [306, 307].

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 [308]. 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 in papillary necrosis, urachal cyst, urethral diverticulum, periurethral 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.

A 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 [309].

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 [310]. 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 [311-313]. 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 [314].

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 [315]. However, if the genitalia are not cleaned and culture is delayed, a high incidence of false-positive results (85-99%) can be found [316, 317].

(2) Clean-catch urine collection: The infant is placed in the lap of a parent 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 [318]. This is time consuming and requires proper instruction of the parents. 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% [318, 319]; however the contamination rate is higher compared to SPA [320].

(3) Bladder catheterisation: In female infants and also in neonates, this technique may be an alternative to SPA, however with a higher contamination rate [321]. 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 [322] 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 [322-324]. Using US to assess bladder filling, simplifies SPA and improves the diagnostic yield of obtaining a urine specimen from 60% to 97% [323, 324]. Complications are rare and have been reported in only 0.22% of cases, ranging from transient haematuria to bowel perforation [325]. However, bladder puncture causes more pain than catheterisation in infants less than two months old [326].

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 [327].

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 [319]. 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 [319, 328]. 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) [319, 329].

Table 1: Sensitivity and specificity of component of urinalysis, alone and in combination [319]*

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 [319].

(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/µL) [325]. In uncentrifuged urine, > 10 WBC/µL has been demonstrated to be sensitive for UTI [330] and this could perform well in clinical situations [331]. 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 [332]. The numbers of WBCs, squamous epithelial cells and red cells correlate well with those found by manual methods [319].

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 [304]. The classical definition of > 10^5 cfu/mL of voided urine is still used to define a significant UTI [333, 334]. The American Academy of Pediatric Guidelines on Urinary Tract Infection suggest that the diagnosis should be 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 [335, 336]. 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 [337])

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) [319]. In other studies, renal US revealed abnormalities in up to 37% of cases, whereas voiding cystourethrography (VCUG) showed VUR in 27% of cases [307]. Dilating VUR is missed by US in around one third of cases [338]. 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 predictis recurrence of UTIs in toilet-trained children [339].

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 [340] 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 [338, 341]. 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 [342]. 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 [343, 344]. Performance of early VCUG in patients with proven sterile urine does not cause any significant morbidity [345]. 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 [346-349]. Treatment of constipation leads to a decrease in UTI recurrence [350-352]. 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 [353, 354].

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 [310, 355, 356].

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 [319]. 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 [355, 357, 358].

3.8.4.2 Duration of therapy

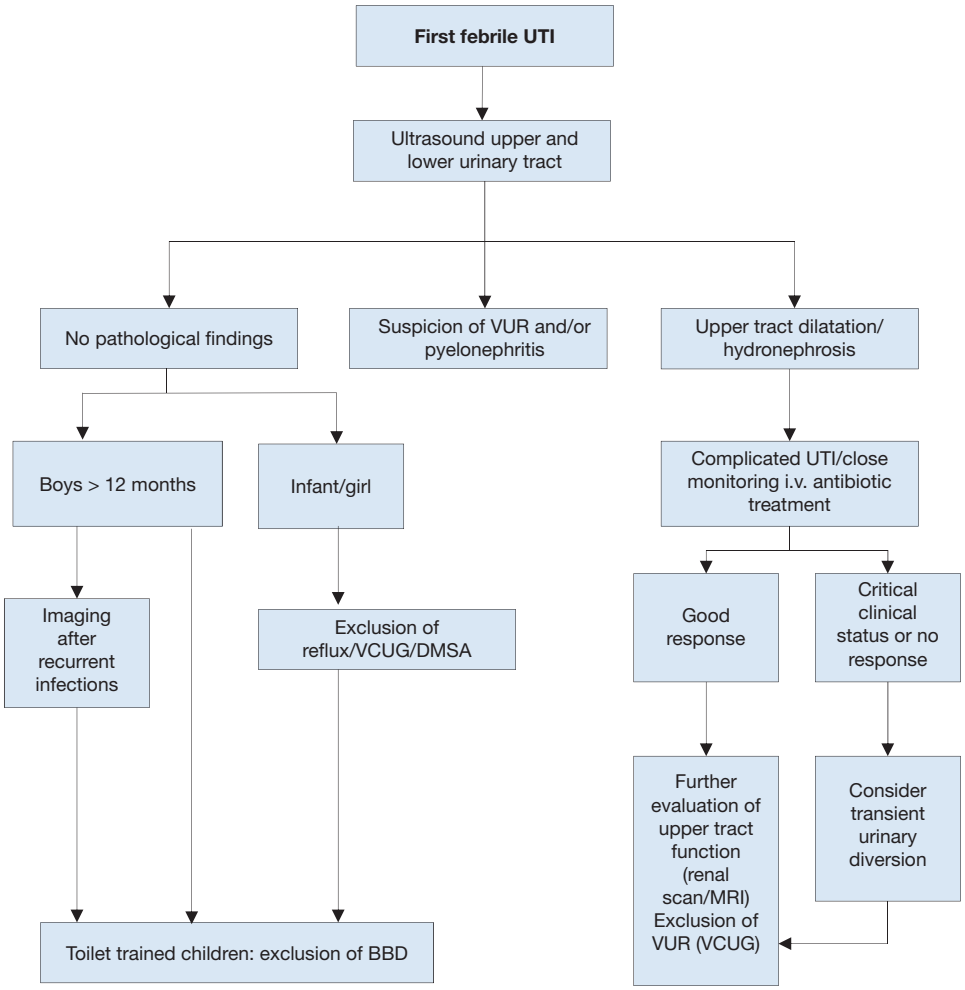
Prompt adequate treatment of UTI can prevent the spread of infection and renal scarring. Outcomes of short courses (one to three days) are inferior to those of seven to fourteen-day courses [319]. In newborns and young infants with a febrile UTI, up to 20% may have a positive blood culture [306, 310]. In late infancy, there are no differences between strategies regarding the incidence of parenchymal scars, as diagnosed with DMSA scan [359]. 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 [356, 360-362]. Similar data have been shown for amoxicillin-clavulanate [363], however, these antibiotics are associated with increasing rates of resistance. 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 [364].

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 [310]. Parenteral treatment with broad-spectrum antibiotics is preferred. A temporary urinary diversion (suprapubic-cystostomy 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 (megaureter).

Prolonged intravenous antibiotic treatment is sufficient in most cases [365], and intravenous and oral therapy tailored to the pathogen identified in culture is recommended [366].

Figure 4: Algorithm for disease management of first febrile UTI



BBD = Bladder Bowel Dysfunction; DMSA = technetium^{99}-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 [367]. There are upcoming reports of UTIs caused by extended spectrum ß-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% [368]. 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 [369].

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

Chemotherapeutics	Daily dosage	Application	Comments
Parenteral cephalosporins			
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	
Oral cephalosporins			
Group 3, e.g. ceftibuten	9 mg/kg *(Adolesc.: 0.4 g)*	p.o. in 1-2 D 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 i.v. in 3-4 D	Ampicillin and Amoxicillin are not eligible for calculated therapy
Amoxicillin	50-100 mg/kg *(Adolesc.: 1.5-6 g)*	p.o. in 2-3 D[1] p.o. in 2-3 D	
Amoxicillin/clavulanic acid (parenteral)	60-100 mg/kg *(Adolesc.: 3.6-6.6 g)*	i.v. in 3 D i.v. in 3 D	
Amoxicillin/clavulanic acid (oral)	45-60 mg/kg *(Amoxicillinfraction)* *(Adolesc.: 1500 + 375 mg)*	p.o. in 3 D p.o.in 3 D	
Piperacillin	300 mg/kg	i.v. in 3-4 D	
Tobramycin	5 mg/kg *(Adolesc.: 3-5 mg/kg, max. 0.4 g)*	i.v. in 1 D	Drug monitoring
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) Children and adolesc. (1-17 years of age): 20-40 mg/kg (max. D 750 mg) (orally)	i.v. in 3 D p.o. in 2 D	Approved in most European countries as second- or third line medication for complicated UTIs, “reserve-antibiotic”!
Nitrofurantoin	3-5 mg	p.o. in 2 D	Contraindicated in the case of renal insufficiency

** Reproduced with permission from the International Consultation on Urological Diseases (ICUD), International Consultation on Urogenital Infections, 2009. Copyright © by the European Association of Urology [370].*
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[1] or Aminoglycoside + Ampicillin[1]	3-7 D parenterally, for at least 2 D after defervescence, then oral therapy[2] In newborns: parenteral therapy for 7-14 D, then oral therapy[2]	10 (-14) D Newborns 14-21 D	4
Uncomplicated pyelonephritis after 6 months of age	Cephalosporin group 3[2]	Orally (initially parenterally, if necessary)	(7-)10 D	1
Complicated pyelonephritis/ urosepsis (all ages)	Ceftazidime + Ampicillin[1] or Aminoglycoside + Ampicillin[1]	7 D parenterally, then oral therapy[2]	10-14 D	4

** Reproduced with permission from the International Consultation on Urological Diseases (ICUD), International Consultation on Urogenital Infections, 2009. Copyright © by the European Association of Urology [370].*
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

** Reproduced with permission from the International Consultation on Urological Diseases (ICUD), International Consultation on Urogenital Infections, 2009. Copyright© by the European Association of Urology [370].*

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 [371-374]. However, two recently published prospective randomised trails as well as one meta-analysis demonstrated a significant risk reduction of developing another UTI by using continuous antibiotic prophylaxis [360, 375, 376] (see also Chapter 3.13 on VUR).

Cranberry juice as well as probiotics may also prevent recurrence of UTI as demonstrated by RCTs [377-379]. A cochrane review could not rule out some benefit of using probiotics [380].

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	***

** Reproduced with permission from the International Consultation on Urological Diseases (ICUD), International Consultation on Urogenital Infections, 2009. Copyright © by the European Association of Urology [370].*
*** 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 [381]. 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 > 10^5 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	GR
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	A
Exclude bladder- and bowel dysfunction in any child with febrile and/or recurrent UTI.	3	A
Do not delay diagnosis and treatment of bladder-bowel-dysfunction.	2a	A
Collect an uncontaminated urine sample in an infant through suprapubic bladder aspiration. Bladder catheterisation is an alternative (traumatic especially in boys).	2a	B
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	B
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	B
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	B
Treat UTIs with four to seven day courses of oral or parenteral therapy. Do not use of short courses (one to three days) since outcomes are inferior.	1b	B
Offer long-term antibacterial prophylaxis in case of high susceptibility to UTI and risk of acquired renal damage and lower urinary tract symptoms (LUTS).	1b	B
Treat complicated UTI, with broad-spectrum antibiotics (parenteral).	1b	B
In infants with febrile UTI, use renal and bladder ultrasound to exclude obstruction of the upper and lower urinary tract.	3	B
In all infants, exclude vesicoureteral reflux (VUR) after the first episode of febrile UTI, using voiding cystourethography (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	B

3.9 Day-time lower urinary tract conditions

*3.9.1 **Epidemiology, aetiology and pathophysiology***

Day-time LUT conditions are conditions that present with LUTS, including urgency, urge incontinence, weak stream, hesitancy, frequency and UTIs without overt uropathy or neuropathy. Following the newest terminology document by the International Children's Continence Society (ICCS), 'day-time LUT conditions' is the new term used to group together functional incontinence problems in children [382]. After any possible underlying uropathy or neuropathy has been excluded, a problem of incontinence in children is grouped into the category of 'day-time LUT conditions'. Night-time wetting is known as 'enuresis'.

Due to the relationship between the bladder and bowel, concomitant bladder and bowel disturbances have been labelled as bladder bowel dysfunction (BBD). The use of the terms dysfunctional elimination syndrome (DES) or voiding dysfunction are discouraged. Bladder bowel dysfunction is an umbrella term that can be subcategorised into LUT dysfunction and bowel dysfunction.

Although exact data are unavailable, it is clear that the incidence of day-time LUT conditions is increasing. Awareness and better access to specialised health care can be one of the reasons for this observation. Reported prevalence ranges widely from 2% to 20% [383-387]. This wide variation might reflect the variation in definitions used. In recent studies, bowel dysfunction is observed in > 50 % of children suffering LUT dysfunction [388, 389].

*3.9.2 **Classification systems***

Various functional disorders of the detrusor-sphincter complex may occur during the sophisticated early development of normal mechanisms of micturition control. Lower urinary tract conditions are therefore thought to be the expression of incomplete or delayed maturation of the bladder sphincter complex. Normal day-time control of bladder function matures between two and three years of age, while night-time control is normally achieved between three and seven years of age [383]. There are two main groups of LUTD, namely, filling-phase dysfunctions and voiding-phase dysfunctions. As compared to the general population, in children LUT conditions present with higher prevalence of comorbidities such as Attention Deficit and Hyperactivity Disorder (ADHD) [390, 391].

3.9.2.1 Filling-phase dysfunctions

In filling-phase dysfunctions, the detrusor can be overactive, as in overactive bladder (OAB), or underactive, as in underactive bladder (UAB). Some children habitually postpone micturition leading to voiding postponement.

3.9.2.2 Voiding-phase (emptying) dysfunctions

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

*3.9.3 **Diagnostic evaluation***

A non-invasive screening, consisting of history-taking, clinical examination, uroflow, US and voiding diary, is essential to reach a diagnosis [391]. In the paediatric age group, where the history is taken from both the parents and child together, a structured approach is recommended using a questionnaire. Many signs and symptoms related to voiding and wetting will be unknown to the parents and should be specifically requested, using the questionnaire as a checklist. A voiding diary is mandatory to determine the child's voiding frequency and voided volumes as well as the child's drinking habits. History-taking should also include assessment of bowel function. Some dysfunctional voiding scores have recently been developed and validated [392, 393]. For evaluation of bowel function in children, the Bristol Stool Scale is an easy-to-use tool [394, 395].

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

In the case of resistance to initial treatment, or in the case of former failed treatment, re-evaluation is warranted and further video-urodynamic (VUD) studies 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 [396] (LE: 1b).

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 further cystoscopy with treatment. If neuropathic disease is suspected, MRI of the lumbosacral spine and medulla can help to exclude tethered cord, lipoma or other rare conditions.

*3.9.4 **Management***

Treatment of LUTD consists of LUT rehabilitation, mostly referred to as urotherapy, meaning non-surgical, non-pharmacological, treatment of LUT function. It is a very broad therapy field, incorporating many treatments used by urotherapists and other healthcare professionals [397]. In case of comorbidity due to bowel problems it is advised to treat the bowel first, since bowel problems may sustain any bladder problems [394]. Urotherapy can be divided into standard therapy and specific interventions. It is strongly advised not to use terms such as "standard therapy" or "maintenance therapy" without defining the design of these treatments.

3.9.4.1 Standard therapy

In case of combined bladder- and bowel dysfunction it is advised to treat the bowel dysfunction first [389] as LUTS may disappear after successful management of bowel dysfunction. Standard urotherapy is defined as non-surgical, non-pharmacological, treatment for LUTD. It can include the following components:

- Information and demystification, which includes explanation about normal LUT function and how a particular child deviates from normal function.
- Instruction about what to do about the problem, i.e. regular voiding habits, sound voiding posture, avoiding holding manoeuvres, etc.
- Lifestyle advice, regarding fluid intake, prevention of constipation, etc.
- Registration of symptoms and voiding habits using bladder diaries or frequency-volume charts.
- Support and encouragement via regular follow-up by the caregiver.

A success rate of 80% has been described for urotherapy programmes, independent of the components of the programme. However, the evidence level is low as most studies of urotherapy programmes are retrospective and non-controlled. A 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 therapy [396] (LE: 1b).

3.9.4.2 *Specific interventions*

As well as urotherapy, there are some specific interventions, including physiotherapy (e.g. pelvic floor exercises), biofeedback, alarm therapy and neurostimulation. Although good results with these treatment modalities have been reported, the level of evidence remains low, since only a few RCTs were published [350, 397-402]. 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 [403, 404]. In some cases, pharmacotherapy may be added. Antispasmodics and anticholinergics have been shown to be effective, although the level of evidence was low. Some studies on orthosypathicomimetics have been published with a low level of evidence [405].

A few RCTs have been published, one on tolterodine showed safety but not efficacy [406], while another on propiverine showed both safety and efficacy [407] (LE: 1). 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 α-blocking agents are used occasionally, an RCT showed no benefit [408]. Botulinum toxin injection seems promising, but can only be used off-label [409]. Other new treatment modalities such as sacral nerve stimulation are described in case series only and there is no evidence for their usefulness. These new treatment modalities can only be recommended for standard therapy resistant cases [410]. A recent ICCS standardisation document on treatment of day-time incontinence gives an excellent overview of treatment modalities [390].

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

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

Recommendations	**LE**	**GR**
Use a stepwise approach, starting with the least invasive treatment in managing day-time lower urinary tract dysfunction (LUTD) in children.	4	B
Initially offer urotherapy involving: non-invasive training and re-education, and non-invasive neurostimulation.	2	B
If present, treat bladder bowel dysfunction bowel dysfunction first, before treating the lower urinary tract condition.	2	B
Use pharmacotherapy (mainly antispasmodics and anticholinergics) as second line therapy.	1	C
Re-evaluate in case of therapy resistance; this may consist of videourodynamics and magnetic resonance imaging of lumbosacral spine, guiding to off-label treatment (e.g. some of the non-licensed drugs in children, botulinum toxin injection and sacral nerve stimulation). Such treatment should only be offered in highly experienced centres.	3	C

3.10 Monosymptomatic enuresis

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

Enuresis is synonymous to intermittent nocturnal incontinence. It is a frequent symptom in children. With a prevalence of 5-10% at seven years of age, it is one of the most prevalent conditions in childhood. With a spontaneous yearly resolution rate of 15%, it is considered relatively benign [411, 412]. Nocturnal enuresis is considered primary when a child has not yet had a prolonged period of being dry. The term "secondary nocturnal enuresis" is used when a child or adult begins wetting again after having stayed dry.

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

Genetically, enuresis is a complex and heterogeneous disorder. Loci have been described on chromosomes 12, 13 and 22 [413].

Three factors play an important pathophysiological role:

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

Due to an imbalance between night-time urine output and night-time bladder capacity, the bladder can become easily full at night and the child will either wake up to empty the bladder or will void during sleep if there is a lack of arousal from sleep [411-413]. Recently, attention has been given to the chronobiology of micturition in which the existence of a circadian clock in kidney, brain and bladder [414] (LE: 1).

*3.10.2 **Classification systems***

Enuresis is the condition describing the symptom of incontinence during night. Any wetting during sleep above the age of five years is enuresis. However, most importantly, there is a single symptom only. Children with other LUTS and enuresis are said to have non-monosymptomatic enuresis [411]. Thorough history-taking, excluding any other day-time symptoms, is mandatory before diagnosing monosymptomatic enuresis. Any associated urinary tract symptoms make the condition a 'day-time LUT condition' [413].

The condition is described as 'primary' when the symptom has always existed and the patient has not been dry for a period longer than six months. The condition is described as 'secondary', when there has been a symptom-free interval of six months.

*3.10.3 **Diagnostic evaluation***

The diagnosis is obtained by history-taking. In a patient with monosymptomatic enuresis, no further investigations are needed. A voiding diary, which records day-time bladder function and night-time urine output, will help to guide the treatment. An estimate of night-time urine production can be obtained by weighing diapers (nappies) in the morning and adding the volume of the morning void. Measuring the day-time bladder capacity gives an estimate of bladder capacity compared to normal values for age [415].

Ultrasound of the urinary tract is not recommended but, when available, it can be used to exclude underlying pathology. In most children, bedwetting is a familial problem, with most affected children found to have a history of bedwetting within the family. A urinary dipstick may help differentiate between true enuresis resulting from polyuria due to diabetes insipidus.

*3.10.4 **Management***

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

3.10.4.1 Supportive treatment measures

Explaining the condition to the child and the parents helps to demystify the problem. 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 has been shown to be successful.

Counselling, provision of information, positive reinforcement, and increasing (and supporting) motivation of the child should be introduced first. A recent Cochrane review shows that simple behavioural interventions can be effective. However, other proven therapies like enuresis alarm and tricyclic antidepressants are more effective [416] (LE:1a).

3.10.4.2 Alarm treatment

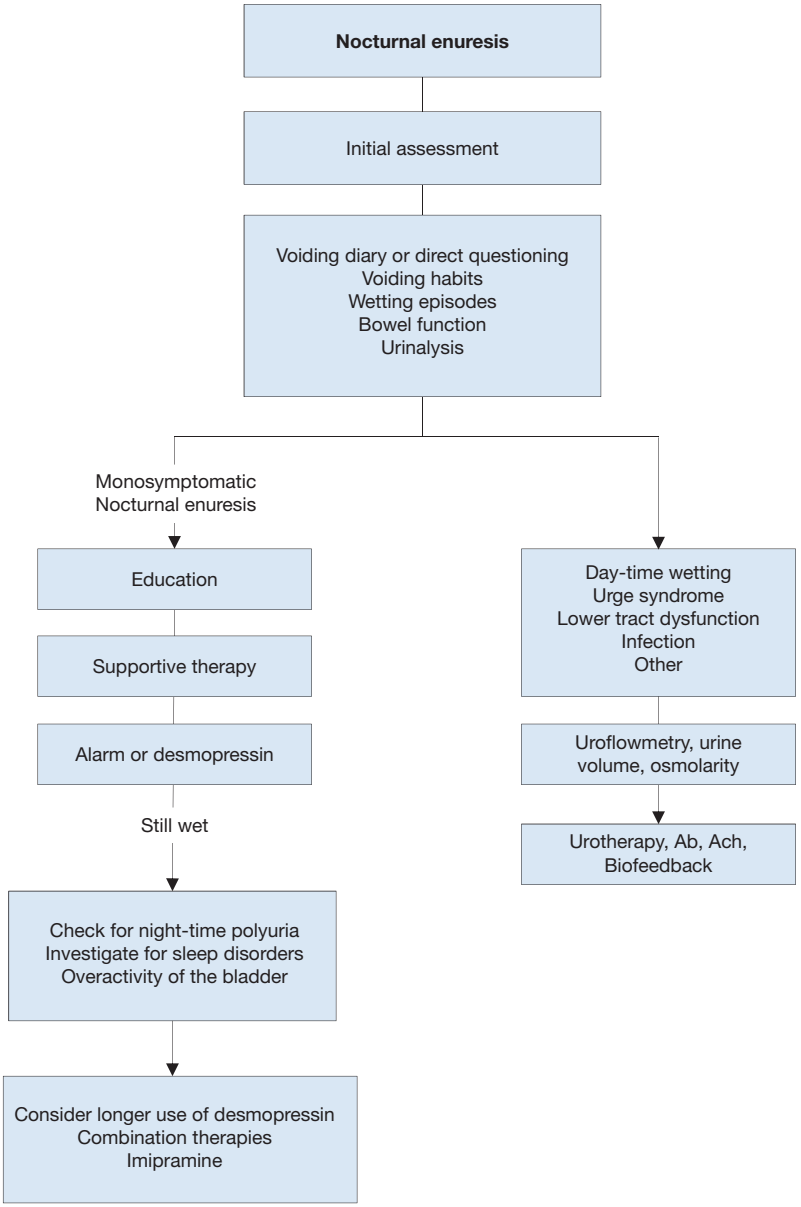
Alarm treatment is the best form for arousal disorder (LE: 1). Initial success rates of 80% are realistic, with low relapse rates, especially when night-time diuresis is not too high and bladder capacity is not too low [417].

3.10.4.3 Medication

In the case of high night-time diuresis, success rates of 70% can be obtained with desmopressin (DDAVP), either as tablets (200-400 µg), or as sublingual DDAVP oral lyophilisate (120-240 µg). A nasal spray is no longer recommended due to the increased risk of overdose [418, 419] (LE: 1). Relapse rates are high after DDAVP discontinuation [415] however recently, structured withdrawal has shown lower relapse rates [420] (LE: 1).

In the case of small bladder capacity, treatment with antispasmodics or anticholinergics is possible [415]. However, when these medications are necessary, the condition is no longer considered to be monosymptomatic. 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 [421] (LE: 1). Figure 5 presents stepwise assessement and management options for nocturnal enuresis.

Figure 5: Assessment and management of nocturnal enuresis



Ab = antibody; Ach = acetylcholine.

3.10.5 *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	GR
Do not treat children less than 5 years of age in whom spontaneous cure is likely.	2	A
Use voiding diaries or questionnaires to exclude day-time symptoms.	2	A
Perform a urine test to exclude the presence of infection or potential causes such as diabetes insipidus.	2	B
Offer supportive measures in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important. When used alone they have limited success.	1	A

Offer alarm treatment for arousal disorder with low relapse rates. There may be family compliance problems.	1	A
Offer desmopressin for the treatment of night-time diuresis. The response rate is high around 70%; relapse rates are high.	1	A
Ensure structured withdrawal of desmopressin to improve relapse rates.	1	A
Ensure that the parents are well informed about the problem. The advantages and disadvantages of each of the two treatment modalities should be explained.The choice of the treatment modality can be made during parental counselling.	4	B

3.11 Management of neurogenic bladder

3.11.1 Epidemiology, aetiology and pathophysiology

Neurogenic detrusor-sphincter dysfunction (NDSD) can develop as a result of a lesion at any level in the nervous system. This condition contributes to various forms of LUTD, which may lead to incontinence, UTIs, VUR, and renal scarring. Surgery may be required to establish adequate bladder storage and drainage. If not managed properly, NDSD can potentially cause renal failure, requiring dialysis or transplantation. The main goals of treatment are prevention of urinary tract deterioration and achievement of continence at an appropriate age.

The management of neurogenic bladder sphincter dysfunction in children has undergone major changes over the years. Although nappies (diapers), permanent catheters, external appliances, Crede's manoeuvre and various forms of urinary diversion have been acceptable treatment methods, these are now reserved for only a small number of resistant patients. The introduction of clean intermittent catheterisation (IC) has revolutionised the management of children with neurogenic bladder. Not only has it made conservative management a very successful treatment option, but it has also made surgical creation of continent reservoirs a very effective treatment alternative, with a good outcome for quality of life and kidney protection [422-424].

Neurogenic bladder in children with myelodysplasia presents with various patterns of DSD with a wide range of severity. About 15% of neonates with myelodysplasia have no signs of neuro-urological dysfunction at birth. However, there is a high chance of progressive changes in the dynamics of neurological lesions with time. Even babies with normal neuro-urological function at birth have a one in three risk of developing either detrusor sphincter dyssynergia or denervation by the time they reach puberty. At birth, the majority of patients have normal UUTs, but nearly 60% of them develop upper tract deterioration due to infections, bladder changes and reflux [425-428].

The most common presentation at birth is myelodysplasia. The term myelodysplasia includes a group of developmental anomalies that result from defects in neural tube closure. Lesions may include spina bifida occulta, meningocele, lipomyelomeningocele, or myelomeningocele. Myelomeningocele is by far the most common defect seen and the most detrimental. Traumatic and neoplastic spinal lesions of the cord are less frequent in children. Additionally, different growth rates between the vertebral bodies and the elongating spinal cord can introduce a dynamic factor to the lesion. Scar tissue surrounding the cord at the site of meningocele closure can tether the cord during growth. In occult myelodysplasia, the lesions are not overt and often occur with no obvious signs of neurological lesion. In nearly 90% of patients, however, a cutaneous abnormality overlies the lower spine, and this condition can easily be detected by simple inspection of the lower back [429].

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

3.11.2 Classification systems

The purpose of any classification system is to facilitate the understanding and management of the underlying pathology. There are various systems of classification of neurogenic bladder.

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

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

The bladder and sphincter are two units working in harmony to make a single functional unit. The initial approach should be to evaluate the state of each unit and define the pattern of bladder dysfunction.

According to the nature of the neurological deficit, the bladder and sphincter may be in either an overactive or inactive state:

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

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

*3.11.3 **Diagnostic evaluation***

3.11.3.1 Urodynamic studies

Since the treatment plan mainly depends upon a good understanding of the underlying problem in the LUT, a well-performed urodynamic study is mandatory in the evaluation of each child with neurogenic bladder. As the bony level often does not correspond with the neurological defect present, and as the effect of the lesion on bladder function cannot be entirely determined by radiographic studies or physical examination, the information gained from a urodynamic study is crucial. A urodynamic study also provides the clinician with information about the response of the vesicourethral unit to therapy, as demonstrated by improvement or deterioration in follow-up.

It is important to determine several urodynamic parameters, including:

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

3.11.3.1.1 Method of urodynamic study

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

3.11.3.1.2 Uroflowmetry

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

Recording of pelvic floor or abdominal skeletal muscle activity by electromyography (EMG) during uroflowmetry can be used to evaluate coordination between detrusor and the sphincter. As it is a non-invasive test, combined uroflowmetry and EMG may be very useful in evaluating sphincter activity during voiding [430-433] (LE: 3; GR: C).

3.11.3.2 Cystometry

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

It is important to be aware of the alterations in filling and emptying detrusor pressures as the infusion rates change during cystometry. Slow fill cystometry (filling rate < 10 mL/min) is recommended by the ICCS for use in children [434]. However, it has been suggested that the infusion rate should be set according to the child's predicted capacity, based on age and divided by 10 or 20 [412].

Several clinical studies using conventional artificial fill cystometry to evaluate neurogenic bladder in children have reported that conventional cystometry provides useful information for diagnosis and follow-up

of children with neurogenic bladder [435-440]. All of the studies were retrospective clinical series and lacked comparison with natural fill cystometry, so that the grade of recommendation for an artificial cystometry in children with neurogenic bladder is not high (LE: 4). Additionally, there is evidence suggesting that natural bladder behaviour is altered during regular artificial filling cystometry [441-444].

Conventional cystometry in infants is useful for predicting future deterioration. Urodynamic parameters, such as low capacity, compliance and high leak-point pressures, are poor prognostic factors for future deterioration. Resolution of reflux is less likely to happen in such bladders [435, 439, 441] (LE: 4). Although there are only a few studies on natural fill cystometry in children with neurogenic bladder, the results suggest that natural fill cystometry detects new findings compared with diagnoses delivered by conventional cystometry [442] (LE: 3). However, the comparison between natural- and artificial fill cystometry has not been performed against a gold standard, making it difficult to conclude which study is a true reflection of natural bladder behaviour. Findings in the non-neurogenic adult population have questioned the reliability of natural fill cystometry, as it has shown a high incidence of bladder over-activity in totally normal asymptomatic volunteers [445]. The main disadvantage of natural fill cystometry is that it is labour-intensive and time-consuming. Moreover, because of the transurethral catheter used during this study, false-positive findings caused by the catheter are possible. Especially in children, the recording of events is difficult and there is an increased risk of artefacts, which makes interpretation of the huge amount of data even more difficult. Natural fill cystometry remains a new technique in the paediatric population. More data need to be gathered in a standard way before it can be widely accepted [433].

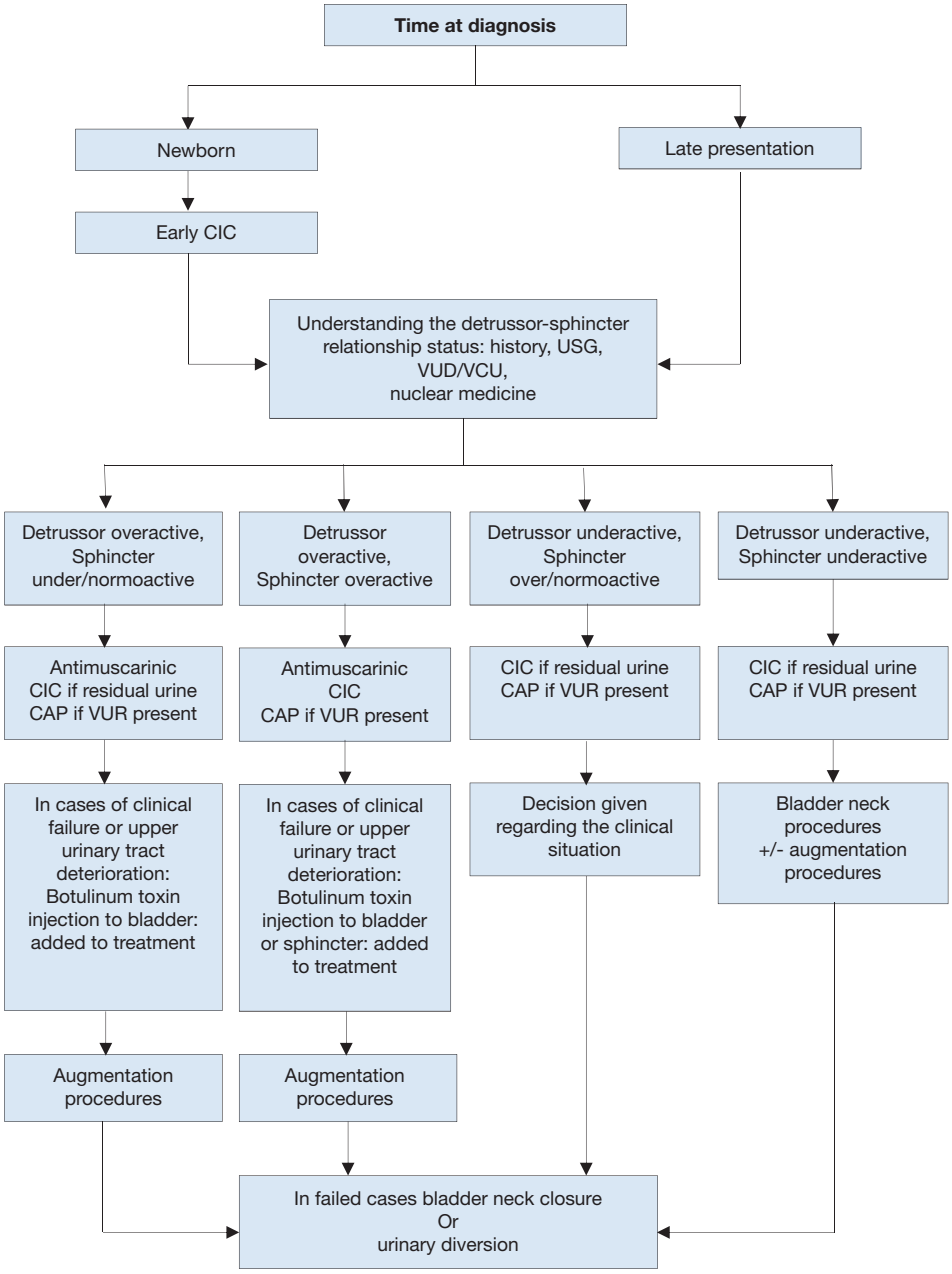
The timing of the first urodynamic study is not clear. However, repeat studies should be done in a child with neurogenic bladder who are not responsive to the initial treatment or in whom a change in treatment or an intervention is planned.

3.11.4 Management

The medical care of children with myelodysplasia with a neurogenic bladder requires constant observation and adaptation to new problems. In the first years of life, the kidneys are highly susceptible to back-pressure and infection. During this period, the emphasis is on documenting the pattern of NDSD and assessing the potential for functional obstruction and VUR. The early study and treatment of patients is essential for decreasing renal impairment, reducing the need for surgery and improving the continence options [446].

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

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



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

3.11.4.1 Investigations

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

A urodynamic evaluation can be done after some weeks, and needs to be repeated at regular intervals, in combination with evaluation of the upper tract [447-449] (LE: 3).

3.11.4.2 Early management with intermittent catheterisation

Overwhelming experience gained over the years with early management of neurogenic bladder in infants has led to a consensus that children do not have upper tract deterioration when managed early with IC and anticholinergic medication. Intermittent catheterisation should be started soon after birth in all babies, especially in those with signs of possible outlet obstruction [349, 447, 450-457] (LE: 2). In babies without any

clear sign of outlet obstruction, may be delayed but these babies should be monitored for UTIs and upper tract changes.

The early initiation of IC in the newborn period makes it easier for parents to master the procedure and for children to accept it, as they grow older [458, 459].

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

Early institution of IC and anticholinergic drugs may prevent this in some patients [424, 457, 460] (LE: 3). The retrospective evaluation of patients has also shown that significantly fewer augmentations were required in patients with an early start of IC [451, 456] (LE: 4).

3.11.4.3 Medical therapy

At present, oxybutynin, tolterodine, trospium and propiverine are the most frequently used drugs, with oxybutynin being the most studied. The dosage for oxybutynin is 0.1-0.3 mg/kg given three times daily. In case of side effects intravesical administration may be considered.

Two different forms of tolterodine have been investigated in children with neurogenic bladder. The extended release formulation of tolterodine has been found to be as efficient as the instant release form, with the advantages of being single dose and less expensive. Although the clinical outcome is encouraging, the level of evidence is low for anticholinergic medication because there are no controlled studies [460-467] (LE: 3). The use of medication to facilitate emptying in children with neurogenic bladder has not been well studied in the literature. A few studies investigating the use of α-adrenergic blockade in children with neurogenic bladder have reported a good response rate, but the studies lacked controls, and long-term follow-up is warranted [468] (LE: 4).

Botulinum toxin injections: In neurogenic bladders that are refractory to anticholinergics, injection of botulinum toxin into the detrusor muscle is a novel treatment alternative. Initial promising results in adults has resulted in its use in children. It has been shown that this treatment has beneficial effects on clinical and urodynamic variables. Complete continence was achieved in 65-87% of patients; in most studies mean maximum detrusor pressure was reduced to at least 40 cmH_2O and bladder compliance was increased to at least 20 cmH_2O/mL. However, findings are limited by the lack of controlled trials and studies involving small patient numbers [409, 469-473]. Botulinum toxin seems to be more effective in bladders with obvious detrusor muscle over-activity, whereas non-compliant bladders without obvious contractions are unlikely to respond [473-478].

The most commonly used dose of botulinum toxin is 10 U/kg with a maximum dose of 200 U. No dose study has been performed in children and there is no evidence regarding the optimal dose. Currently, it is unclear how many times this treatment can be repeated, although repetitive treatment has been found to be safe in adults [409, 479-481].

Injection of botulinum toxin in therapy-resistant bladders appears to be an effective and safe treatment alternative (LE: 3). Urethral sphincter botulinum-A toxin injection has been shown to be effective in decreasing urethral resistance and improve voiding. The evidence is still too low to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases [482, 483].

3.11.4.4 Management of bowel incontinence

Children with neurogenic bladder have disturbances of bowel function as well as urinary function. Bowel incontinence in these children is frequently unpredictable. It is related to the turnover rate of faecal material in the anal area after evacuation, the degree of intactness of sacral cord sensation and motor function, and reflex reactivity of the external anal sphincter [484].

Bowel incontinence is managed most commonly with mild laxatives, such as mineral oil, combined with enemas to facilitate removal of bowel contents. A regular and efficient bowel emptying regimen is often necessary to maintain faecal continence, and may have to be started at a very young age. With antegrade or retrograde enemas, most children will have decreased constipation problems and may attain some degree of faecal continence [485-489] (LE: 3).

Biofeedback training programmes to strengthen the external anal sphincter have not been shown to be more effective than a conventional bowel management programme in achieving faecal continence [490]. Electrostimulation of the bowel may also offer a variable improvement in some patients [491] (LE: 3).

3.11.4.5 Urinary tract infection

Urinary tract infections are common in children with neurogenic bladders. In the absence of reflux, UTIs should be treated symptomatically. Although bacteriuria is seen in more than half of children on CIC, patients who

are asymptomatic do not need treatment [492-494] (LE: 3). Patients with VUR should usually be placed on prophylactic antibiotics to reduce the incidence of pyelonephritis, which can potentially lead to renal damage [495, 496].

3.11.4.6 Sexuality

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

3.11.4.7 Bladder augmentation

Children with a good response to anticholinergic treatment and an overactive sphincter may be continent between catheterisations. Bladder pressure and development of the UUT will determine whether additional treatment is necessary or not. Therapy-resistant overactivity of the detrusor, or small capacity and poor compliance, will usually need to be treated by bladder augmentation. A simple bladder augmentation using intestine may be carried out if there is any bladder tissue, a competent sphincter and/or bladder neck, and a urethra that can be catheterised.

Stomach is rarely used as an augmenting patch because of the associated complications [497]. Ileal or colonic patches are frequently used for augmenting the bladder, with either equally useful. Despite some advantages (e.g. avoiding mucus, decreased malignancy rate and fewer complications), alternative urothelium preserving techniques, such as autoaugmentation and seromuscular cystoplasty, have not proven to be as successful as standard augmentation with intestine [498, 499].

3.11.4.8 Bladder outlet procedures

Children with detrusor overactivity and underactive sphincters will have better protection of their upper tracts, although they will be severely incontinent. Initial treatment is IC (as it might reduce the degree of incontinence and offers much better control over UTIs) with anticholinergic drugs. At a later age, the outlet resistance will be increased in order to render them continent. No available medical treatment has been validated to increase bladder outlet resistance. α-adrenergic receptor stimulation of the bladder neck has not been very effective [500-505].

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

Various procedures can be used on the bladder neck to increase resistance, but all of them may complicate transurethral catheterisation. Augmentation with surgical closure of the bladder neck may be required primarily, or as a secondary procedure in certain rare clinical situations. In this situation, a continent stoma will be required. However, most surgeons prefer to leave the bladder neck and urethra patent as a safety precaution. Application of artificial urinary sphincters (AUS) in children is another option, which gives the patient the opportunity to void spontaneously. The largest paediatric series in the literature reports a continence rate over 85% [506]. However, the decision to implant an AUS in a child raises the issue of mechanical failure (> 30%), revision of the functioning sphincter (> 15%) and surgical complication (15%). Although, advancement of newer devices decreased these numbers [506].

3.11.4.9 Continent stoma

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

3.11.4.10 Total bladder replacement

Total bladder replacement in anticipation of normal voiding in children is very rare, as there are infrequent indications for a total cystectomy, with preservation of the bladder outlet and a competent urethral sphincter. This type of bladder replacement is much more common in adult urological reconstruction. Any type of major bladder and bladder outlet construction should be performed in centres with sufficient experience in the surgical technique, and with experienced healthcare personnel to carry out post-operative follow-up [507-509].

3.11.5 *Follow-up*

Neurogenic bladder patients require lifelong supervision, and the monitoring of renal and bladder function is extremely important. Periodic investigation of upper tract changes, renal function and bladder status is mandatory. Repeat urodynamic tests are therefore needed more frequently (every year) in younger children and less frequently in older children. From the urological viewpoint, a repeat urodynamic study is warranted when the patient has a change in symptoms or undergoes any neurosurgical procedure. In the case of any apparent changes in the UUT and LUT, or changes in neurological symptoms, a more detailed examination including urodynamics and spinal MRI is indicated.

Renal failure can progress slowly or occur with startling speed in these children. Patients who have undergone reconstructive procedures using intestine should be regularly followed up for complications such as infection, stone formation, reservoir rupture, metabolic changes, and malignancy [507].

The risk of malignancy in enteric augmentations has been reported to be higher than expected, and the risk increases with length of follow-up. Malignancy occurs in 0.6-2.8% of patients during median follow-up of 13-21 years [510-515]. In a study including 153 patients with a median follow-up time of 28 years [512], malignancy was found in 4.5%. The malignancy seemed to be associated with coexisting carcinogenic stimuli or with the inherent risk present with bladder exstrophy. Although there are poor data on follow-up schemes; after a reasonable follow-up time (e.g. ten years), an annual diagnostic work-up including cystoscopy should be considered.

3.11.6 *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	GR
In all babies, start intermittent catheterisation soon after birth, except for babies without any clear sign of outlet obstruction. If intermittent catheterisation is delayed, closely monitor babies for urinary tract infections and upper tract changes.	2	B
Use anticholinergic drugs as initial treatment in children with overactive bladders. Clinical improvement is common but usually insufficient.	2	B
Use injection of botulinum toxin into the detrusor muscle as an alternative in childen who are refractory to anticholinergics.	2	B
Use a bladder augmentation procedure, using a segment of intestine, in case of therapy-resistant overactivity of the detrusor, or small capacity and poor compliance causing upper tract damage and incontinence.	2	B
Use augmentation with additional bladder outlet procedures when both the bladder and outlet are deficient. Simple augmentation will suffice in most low-capacity, high-pressure bladders.	3	B
Augment with an additional continent stoma after bladder outlet surgery and in patients with urethral catheterisation limitations.	3	B
Follow-up of neurogenic bladder patients will be life-long. Follow-up includes monitoring of renal and bladder function as well as ensuring that sexuality and fertility issues receive particular care as the child gets older and moves into adulthood.	3	B

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 [516]. 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 [517].

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 [518].

*3.12.2 **Diagnostic evaluation***

The widespread use of US during pregnancy has resulted in a higher detection rate for antenatal hydronephrosis [519]. 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 non-obstructive 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 28th 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 [520].

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 [521]. 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:

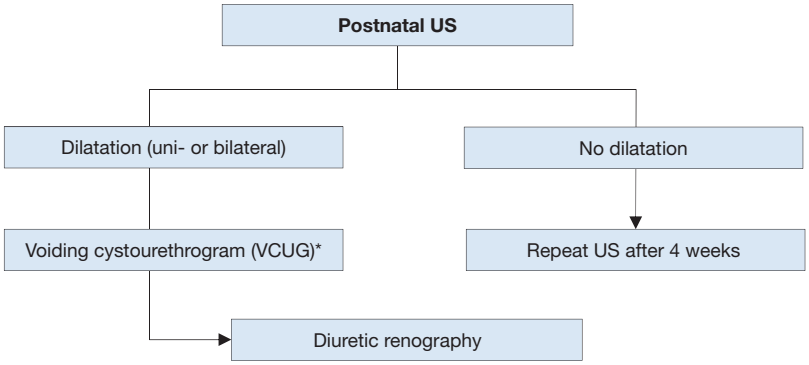
- vesicoureteral reflux (found in up to 25% of affected children) [522];
- urethral valves;
- ureteroceles;
- diverticula;
- neurogenic bladder.

Conventional VCUG is the method of choice for primary diagnostic procedures [523].

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) mercaptoacetyltriglycine (MAG3) is the radionuclide of choice. It is important to perform the study under standardised circumstances (hydration, transurethral catheter) after the fourth and sixth weeks of life [524]. 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 [525]. 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 parents, 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 [522].*
US = ultrasound.

3.12.3 Management
3.12.3.1 Prenatal management
Counselling the parents 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 parents 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 [526].

3.12.3.1.1 Antibiotic prophylaxis for antenatal hydronephrosis (ANH)
The benefits and harms of continous 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 [527] and the other publication is only available as a congress abstract [528]. Both publications present incomplete data and outcomes.

The EAU Paediatric Guidelines Panel conducted a systematic review (SR) assessing the literature from 1980 onwards [4]. 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 ANH. In the first RCT, a prospective longitudinal study [527], 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 [528]. 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 [527].

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 [529]. In experienced hands, laparoscopic or retro-peritoneoscopic 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 [530].

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 [531, 532]. 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 [533]. Robotic-assisted laparoscopic pyeloplasty (RALP) has all the same advantages as LP plus better maneuverability, improved vision, ease in suturing and increased ergonomics but higher costs [534, 535]. 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 [536]. 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 [537].

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 [538]. Data suggest that children with a ureteric diameter of > 10-15 mm are more likely to require intervention [539].

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 [540]. 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	GR
Include serial ultrasound (US) and subsequent diuretic renogram and sometimes voiding cystourehrography (VCUG) in postnatal investigations.	2	B
Offer continuous antibiotic prophylaxis to the sub-group of children with antenatal hydronephrosis who are at high risk of developing urinary tract infection (uncircumcised infants (LE: 1a), children diagnosed with hydroureteronephrosis (LE: 2) and high-grade hydronephrosis (LE: 2)).	2	A
Decide on surgical intervention based on the time course of the hydronephrosis and the impairment of renal function.	2	B
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	B
Offer pyeloplasty when ureteropelvic junction obstruction has been confirmed clinically or with serial imaging studies.	2	B
Do not offer surgery as a standard for primary megaureters since most do not require surgical intervention.	2	B

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. Fortunately, 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 [541]. 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% [542]. Among infants prenatally identified with hydronephrosis on US, who were screened for VUR, the prevalence was 16.2% (7-35%) [543]. 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%) [543].

However, reflux detected by sibling screening is associated with lower grades [543] and significantly earlier resolution [544]. 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 [545, 546].

The incidence of VUR is much higher among children with UTIs (30-50%, depending on age). UTIs 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 [547-550].

There is a clear co-prevalence between LUTD and VUR [347]. 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 that may be accompanied with bowel problems [347]. Some studies have described a prevalence of 40-60% for VUR in children with LUTD [551]. A recently 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 [552].

The spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical presentation, and anatomy [544]. 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 [552-554].

The presence of renal cortical abnormality, bladder dysfunction, and breakthrough febrile UTIs are negative predictive factors for reflux resolution [555-557].

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 [558-560].

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 [561-566], whereas in patients with LUTD, this may increase up to 30% [560, 567, 568]. 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 [569].

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 [570]. In 1985, the International Reflux Study Committee introduced a uniform system for the classification of VUR [571, 572] (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 [572].

Radionuclide studies for detection of reflux have lower radiation exposure than VCUG, but the anatomical details depicted are inferior [573]. Recent studies on alternative imaging modalities for detection on VUR have yielded good results with voiding US and magnetic resonance VCUG [574-576]. 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 [577]

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

Dimercaptosuccinic acid is the best nuclear agent for visualising the cortical tissue and differential function between both kidneys. Dimercaptosuccinic acid is taken up by proximal renal tubular cells and is a good indicator of renal parenchyma function. In areas of acute inflammation or scarring, Dimercaptosuccinic acid 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 [572, 578]. DMSA can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis [579]. Children with a normal DMSA scan during acute UTI have a low-risk of renal damage [579].

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) [347]. 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 [580, 581].

Ultrasound should be delayed until after 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 [561, 582]. 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 [543]. 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 [543]. 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 [543, 563, 583, 584]. When infants who are diagnosed with prenatal hydronephrosis become symptomatic with UTIs, further evaluation with VCUG should be considered [584]. 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. 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%). Early screening and therefore early diagnosis and treatment appears to be more effective than late screening in preventing further renal damage [543, 545, 585, 586]. 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	**GR**
Inform parents of children with vesicoureteric reflux (VUR) that siblings and offspring have a high prevalence of VUR.	A
Use renal ultrasound (US) for screening of sibling(s).	A
Use voiding cystourethrography (VCUG) if there is evidence of renal scarring on US or a history of urinary tract infection.	B
Do not screen older toilet-trained children since there is no added value in screening for VUR.	B

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 ultrasonographic findings may have higher risk of developing renal scars and they should all be evaluated for reflux [587]. 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 [341, 588-590].

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 [552, 591]. 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:

- VUR 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 [592].
- VUR 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 [567, 591, 593-595].
- 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 [596].

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 [567, 597-599]. Trials show the benefit of CAP is none or minimal in low-grade reflux. Continuous anitbiotic 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 [371-374, 600, 601]. The RIVUR trial was the largest, randomised, placebo-controlled, double blind, multi-centre 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 [376, 602-604].

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. CAP 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 parents. 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 reimplantation.

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) [605, 606].

Although the best results have been obtained with PTFE [607], due to concerns about particle migration, PTFE has not been approved for use in children [608]. 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 [609]. 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 [597].

In a meta-analysis [610] 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%) [611]. 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%) [612].

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 antireflux procedure may be considered, because

simultaneous bilateral extravesical reflux repair carries an increased risk of temporary post-operative urine retention [613]. 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 reimplantation, 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 [614, 615].

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 parents in centres where there is established experience [596, 614, 616-623].

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

Summary of evidence	LE
There is no evidence that correction of persistent low-grade reflux (grades I-III) without symptoms and normal kidneys offers a significant benefit.	4
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.	2
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.	2
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.	2

Recommendations	GR
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.	C
Offer immediate, parenteral antibiotic treatment for febrile breakthrough infections.	A
Offer definitive surgical or endoscopic correction to patients with frequent breakthrough infections.	A
Offer surgical correction to patients with persistent high-grade reflux (grades IV/V) if intervention is needed; 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.	B
Initially manage all children presenting at age one to five years conservatively.	B
Offer surgical repair to children presenting with high-grade reflux or abnormal renal parenchyma.	B
Offer close surveillance without antibiotic prophylaxis to children presenting with lower grades of reflux and without symptoms.	B
Ensure that a detailed investigation for the presence of lower urinary tract dysfunction (LUTD) is done in all children after toilet-training. If LUTD is found, the initial treatment should always be for LUTD.	A
Consider surgical correction, if parents prefer definitive therapy to conservative management. Endoscopic treatment is an option for all children with low grades of reflux.	B

Select the most appropriate management option based on : • the presence of renal scars; • clinical course; • the grade of reflux; • ipsilateral renal function; • bilaterality; • bladder function; • associated anomalies of the urinary tract; • age and gender; • compliance; • parental preference.	A
In high-risk patients who already have renal impairment, a more aggressive, multi-disciplinary approach is needed.	A

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. Because of its recurrent nature, every effort should be made to discover the underlying metabolic abnormality so that it can be treated appropriately. Obtaining a stone-free state with close follow-up are of the utmost importance, although, it may not be possible in some circumstances (e.g. oxalosis or nephrocalcinosis).

However, bladder stones are still common in underdeveloped areas of the world and are usually ammonium acid urate and uric acid stones, strongly implicating dietary factors [624]. Patients with augmented bladder constitute another important group with a risk of up to 15% [625].

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 [626-628], especially in girls, Caucasian ethnicity, African Americans and older children [629]. More than 70% of stones in children contain calcium oxalate, while infection stones are found more frequently in younger children [630].

*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 [631].

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) [632].

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 [631, 632]. 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 [631-634]. 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 [635]. 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 [636] (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 [637-640] (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 [637, 641] (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^2/day [642-644], 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 [637, 645] (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 [646-648].

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 [648, 649].

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 [647] (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 [637].

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 [637]. 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 cystine precipitation beginning at pH levels < 7.0. Other metabolic conditions, such as hypercalciuria, hypocitraturia and hyperuricosuria, may accompany cystinuria, so leading to the formation of mixed-composition stones. Cystine stones are faintly 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 [650] (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 [651] and in non-endemic regions [630, 652]. 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 [653, 654].

3.14.3.1 Imaging

Generally, US should be used as a first study. 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 [655-657] (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 [658]. 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

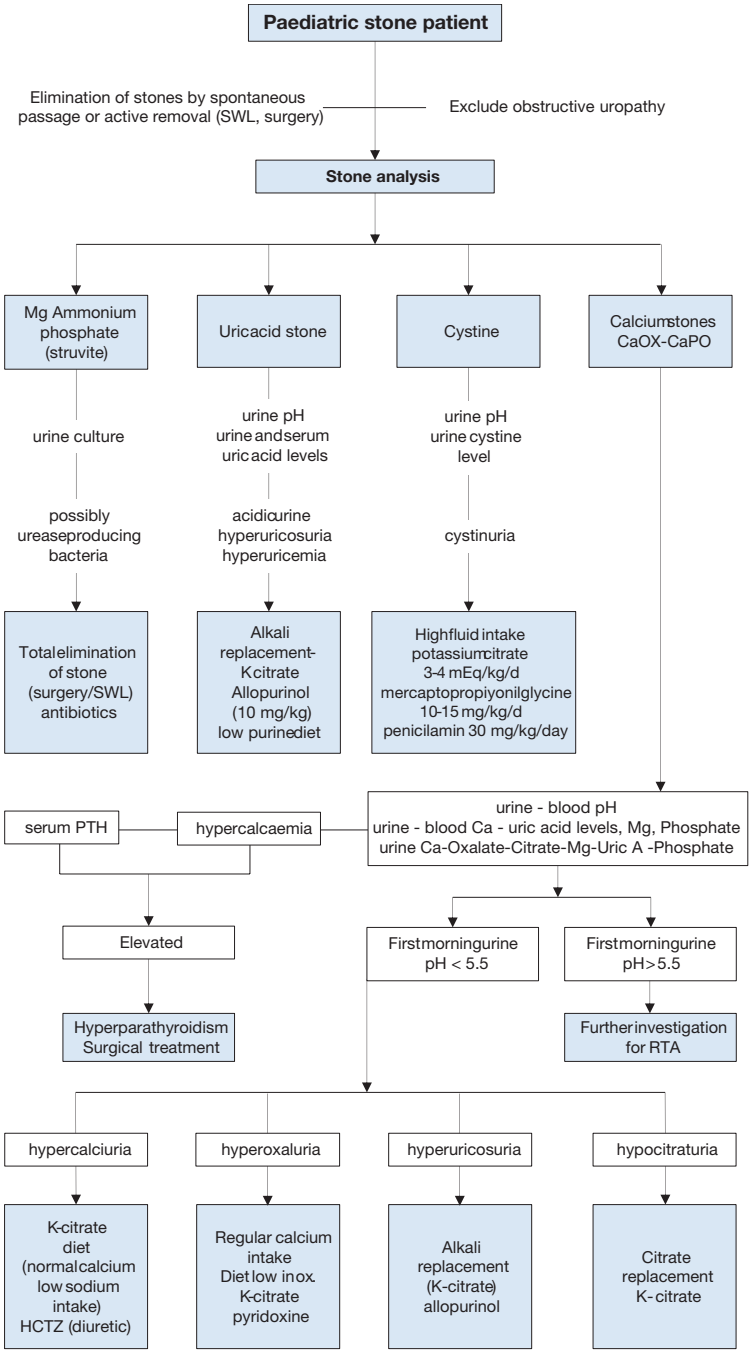
Due to the high incidence of predisposing factors for urolithiasis in children and high stone recurrence rates, every child with urinary stone should be given a complete metabolic evaluation [624, 659-661].

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 = axalate; PTH = parathyroid hormone; SWL = extracorporeal shockwave lithotripsy; RTA = renal tubular acidosis; Uric-A = uric acid.

*3.14.4 **Management***

With the advance of technology stone management has changed from open surgical approaches to endoscopic techniques that are less invasive. Deciding the type of treatment depends on the number, size, location, stone composition and the anatomy of the urinary tract [659, 662, 663]. 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 α-blockers. Although, experience in children is limited showing different results [664], 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 [665]. Currently, most paediatric stones can easily be managed by shockwave lithotripsy (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 [666, 667]. 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 [668-675].

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 [662, 676, 677]. 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 [678] (LE: 2b).

Stone-free rates are significantly affected by various factors. Regardless of the location, as the stone size increases, the stone-free rates decrease and re-treatment rate increases. The stone-free rates for < 1 cm, 1-2 cm, > 2 cm and overall, were reported as nearly 90%, 80%, 60% and 80%, respectively. As the stone size increases, the need for additional sessions increases [662, 676, 677, 679-683].

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% [684-687].

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 [684-686, 688, 689].

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 [682].

Although stenting does not affect stone clearance, overall complication rates are higher and hospital stay is longer in the unstented patient [681, 682]. 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 [660, 683].

The Hounsefield 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 [667] and 1000 [690]. 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 [691, 692].

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 [693]. However, every effort should be made to sterilise the urine before performing SWL, ureteroscopy (URS), or percutaneous nephrolithotomy (PNL).

Because of the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [694-703].

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 [693, 704, 705].

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 [694, 706-710].

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% [711-716] and is closely associated with stone burden, operative time, sheath size and the number of tracts [711, 717, 718]. In recent studies, post-operative infectious complications, such as fever with or without documented UTI, are reported as less than 15% [711-713, 715, 716, 719] 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 [704, 720, 721] as well as ultramini-PCNL (UMP) through 12F sheaths [722] have become possible, with decreased transfusion rates [720]. 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 [723]. 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 [724] (LE: 3, GR: B). For stones 10-20 mm, micro-PNL was shown to have comparable results, with lesser bleeding, compared to mini-PCNL [725] (LE: 3, GR: B). 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 smaller than 2 cm, with patients left either with an indwelling catheter or double J stent in the ureter [714, 719] or totally tubeless [726]. Moreover, use of ultrasonography for establishment of access [727] and supine approach [728] 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; GR:B) [713-728].

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 [693, 695, 696, 729-732] (LE: 3; GR: B).

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, have all been shown to be safe and effective. Because of the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [694-703].

All studies reporting the use of endoscopy for ureteric stones in children have clearly demonstrated that there is no significant risk of ureteric strictures or reflux with this mode of therapy (LE: 1; GR: A). The risk of post-operative hydronephrosis depends on the presence of impacted stone and ureteral injury during operation [733]. 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 [734].

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 [735-739]. 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 [736, 737]. 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 [735, 737-740]. The need for additional procedures was related to stone size [739]. A comparative study showed that retrograde intrarenal surgery (RIRS) had similar stone-free rate compared to ESWL after three months, with fewer sessions [741], however for stones larger than 2 cm, RIRS monotherapy has lower stone-free rates than mini-PCNL with the advantages of of decreased radiation exposure, fewer complications and shorter hospital stay [742] (LE: 3; GR: B). 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 [743] (LE: 3; GR: B).

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 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 [744-747].

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 advantage and disadvantage 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. 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	LE	GR	Secondary treatment options	Comment
Staghorn stones	PCNL	2b	B	Open/SWL	Multiple sessions and accesses with PCNL may be needed. Combination with SWL may be useful.
Pelvis < 10 mm	SWL	2b	B	RIRS/PCNL/MicroPerc	
Pelvis 10-20 mm	SWL	2b	B	PCNL/RIRS/MicroPerc/ Open	Multiple sessions with SWL may be needed. PCNL has similar recommendation grade.
Pelvis > 20 mm	PCNL	2b	B	SWL/Open	Multiple sessions with SWL may be needed.
Lower pole calyx < 10 mm	SWL	2b	B	RIRS/PCNL/MicroPerc	Anatomical variations are important for complete clearance after SWL.
Lower pole calyx > 10 mm	PCNL	2b	B	SWL/ MicroPerc	Anatomical variations are important for complete clearance after SWL.
Upper ureteric stones	SWL	2b	B	PCNL/URS/Open	
Lower ureteric stones	URS	2a	A	SWL/Open	Additional intervention need is high with SWL.
Bladder stones	Endoscopic	2b	B		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	GR
Use plain abdominal X-ray and ultrasound (US) as the primary imaging techniques for the diagnosis and follow-up of stones.	2b	B
Use low-dose non-contrast computed tomography (CT) in cases with a doubtful diagnosis, especially of ureteral stones or complex cases requiring surgery.	2a	B
Perform a metabolic and anatomical evaluation in any child with urinary stone disease.	2a	B
Any kind of interventional treatment should be supported with medical treatment for the underlying metabolic abnormality, if detected.	2a	B
Open surgery may be done under circumstances in which the child is very young with large stones, in association with congenital problems requiring surgical correction and/or with severe orthopedic deformities that limit positioning for endoscopic procedures.	2a	B
Use appropriately-sized instruments in order to decrease the number of complications during surgical treatment.	2b	B

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 4-7 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 [748].

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, 1:5). Some remain asymptomatic, therefore, the true incidence is difficult to determine [749]. 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 [750].

*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 [751-753]. 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 [754, 755]. Vesicoureteral reflux can be observed in 50% on the ipsilateral side and 20% on the contralateral side. Reflux into the ureterocele is uncommon [756]. In the ectopic form, the upper pole is altered, frequently dysplastic, and hypo-functional or non-functional [757, 758]. 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.

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 megaureter. A contralateral renal duplication is associated in 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 [759]:

- 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 [759]:

- 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 [760, 761]. 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 [762-764]. Magnetic resonance urography may visualise the morphological status of the upper pole and lower moieties and of the contralateral kidney, but cannot reliably predict histology [765]. 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 [766]. 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 [767].
- 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 [768]. In some cases, the large ectopic ureter presses against the bladder and can look like a pseudo-ureterocele [769, 770].

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 the most sensitive method [771]. Filling the bladder with methylene blue and checking for clear urine output from the vagina can give clear evidence of extra-sphincteric ureteral ectopia. This test is also helpful in confirming a vesicovaginal fistula (in this case blue fluid drains from the vagina).

*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 [772-777]. 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 parents' and surgeon's preferences [778]. When the diagnosis is made by US, prophylactic antibiotic treatment is 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

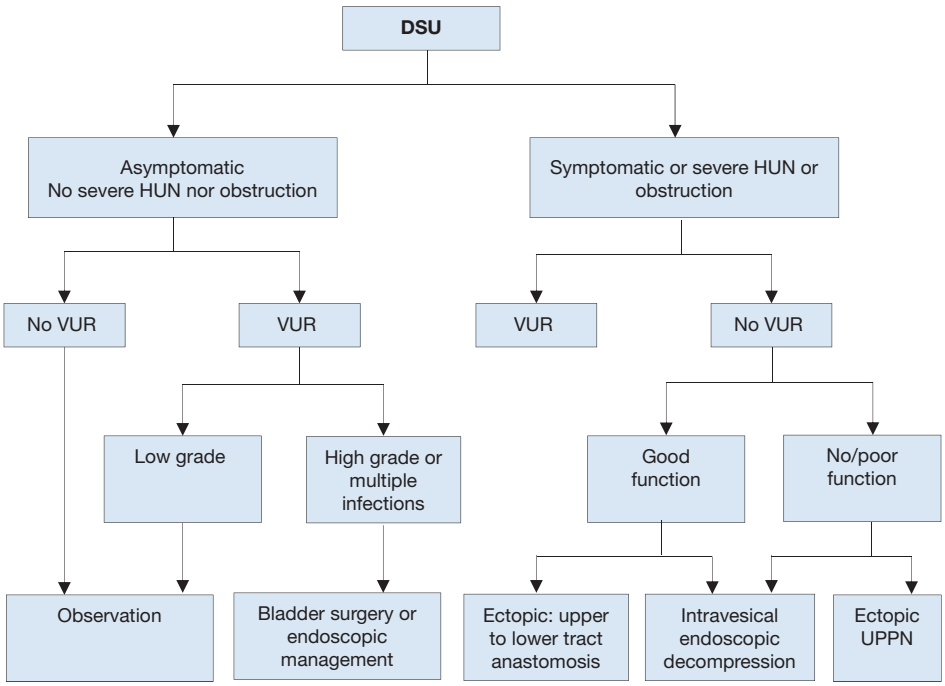
or hypofunctional upper pole, without significant obstruction of the lower pole and without bladder outlet obstruction, prophylactic antibiotic treatment is given until follow-up procedures are instigated.

3.15.4.1.2 Re-evaluation

Conservative treatment may be adopted in asymptomatic patients without any bladder outlet obstruction, severe hydroureteronephrosis of the ureterocele moiety or high-grade (over grade III) reflux [778, 779]. If decompression is effective and there is no reflux (~25% of cases and more often in intravesical ureterocele), the patient is followed-up conservatively. After an endoscopic incision, most of the children with an extravesical ureterocele (50-80%) need a secondary procedure, compared with only 18% of those with an intravesical ureterocele [750]. 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 [780].

Surgery may vary from upper pole nephrectomy to complete unilateral LUT reconstruction [756, 776, 781-784]. In an ectopic ureterocele with severe hydroureteronephrosis 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 [778, 785].

Figure 9: Algorithm for the management of duplex system ureteroceles after the first 3-6 months of life [778]



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 heminephro-ureterectomy should be considered. Ureteral reconstruction (ureteral re-implantation/ureteroureterostomy/ureteropyelostomy and upper-pole ureterectomy) is a therapeutic option in cases in which the upper pole has function worth preserving. Both procedures can be performed through an open or laparoscopic approach [786-788]. 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 [789-792].

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: • 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 parents' and surgeon's preferences.	3

Recommendations			LE	GR
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	B
	Treatment	Select treatment based on symptoms, function and reflux as well on surgical and parenteral choices: observation, endoscopic decompression, ureteral re-implantation, partial nephroureterectomy, complete primary reconstruction.	3	B
		Offer conservative treatment to patients (single/duplex systems) with no hydronephrosis and no symptoms, the risk for renal injury is low and conservative treatment is a good option.		
		Offer endoscopic treatment to patients with reflux; open re-implantation especially in dilating reflux provides better results.		
		Offer, early endoscopic decompression to patients with an obstructing ureterocele. In half to two-thirds of children with an extravesical ureterocele a secondary procedure is needed (compared to 20-25% of those with an intravesical ureterocele).		
		Offer heminephrectomy to patients with a non-functioning moiety and symptoms.		
Ectopic ureter	Diagnosis	Use US, DMSA scan, VCUG or MRI for a definitive diagnosis.	3	B
	Treatment	Select the most appropriate treatment option based on the function of the upper urinary tract.	3	B
		Offer (hemi-)nephroureterectomy in poorly or non-functioning moieties.		
		Offer ureteral re-implantation, ureteroureterostomy or ureteropyelostomy to patients with a functioning renal moiety, especially in cases in which the upper pole has function worth preserving.		

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) [793, 794].

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 as a separate heading.

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

Overall, there is a low evidence base 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 LE 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 [795, 796].

The diagnosis and treatment of DSD requires a multi-disciplinary 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 SD below the mean [793, 794, 797].

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 [793]. The corpora cavernosa are palpated, the scrotum is often small, and the testes may be small and descended. Micropenis should be distinguished from buried and webbed penis, which is usually of normal size. The initial evaluation has to define whether the aetiology of the micropenis is central (hypothalamic/pituitary) or testicular. A paediatric endocrinology work-up has to be carried out immediately. Karyotyping is mandatory in all patients with a micropenis. Endocrine testicular function is assessed (baseline and stimulated testosterone, LH and FSH serum levels). Stimulated hormone levels may also give an idea of the growth potential of the penis. In patients with non-palpable testes and hypogonadotropic hypogonadism, laparoscopy should be carried out to confirm vanishing testes syndrome or intra-abdominal undescended hypoplastic testes. This investigation can be delayed until the age of one year [794].

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 [798-801] (LE: 2). In the presence of androgen insensitivity, good outcome of sexual function is questioned and gender conversion can be considered [802-804].

*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 parents 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)

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

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

History (family, maternal, neonatal)
Parental consanguinity
Previous DSD or genital anomalies
Previous neonatal deaths
Primary amenorrhoea or infertility in other family members
Maternal exposure to androgens
Failure to thrive, vomiting, diarrhoea of the neonate
Physical examination
Pigmentation of genital and areolar area
Hypospadias or urogenital sinus
Size of phallus
Palpable and/or symmetrical gonads
Blood pressure
Investigations
Blood analysis: 17-hydroxyprogesterone, electrolytes, LH, FSH, TST, cortisol, ACTH
Urine: adrenal steroids
Karyotype
Ultrasound
Genitogram
hCG stimulation test
Androgen-binding studies
Endoscopy

ACTH = adrenocorticotropic 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;
- ultrasound to evaluate the presence of Müllerian duct structures.

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

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

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 aspect;
- 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
• Clinical examination • Ultrasound • Genitography • Cystoscopy • Diagnostic laparoscopy
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 a 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 46XXDSD.

Medical photography can be useful but requires sensitivity and consent [805].

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 Mülllerian structures can be evaluated. Is there a vagina? Are there some abdominal gonads? Is there a vaginal or utriculur structure visible [806, 807]?

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 [808, 809].

3.16.3 ***Management***

Referring to the consensus document [793, 794], 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 [810].

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 SPU have taken a position in the debate on surgery for DSD [811].

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 [812, 813]. Informed parental consent should be obtained. Although some techniques that conserve erectile tissue have been described, the long-term outcome is unknown [814].

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 [815, 816].

Vaginoplasty should be performed during the teenage years. Every technique (self-dilatation, skin or bowel substitution) has its specific advantages and disadvantages [817]. 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 [818].

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	GR
Treat disorders of sex development (DSD) within a multi-disciplinary team.	A
Refer children to experienced centres where neonatology, paediatric endocrinology, paediatric urology, child psychology and transition to adult care are guaranteed.	A
Do not delay treatment of any neonate presenting with ambiguous genitalia since salt-loss in a 46XX CAH girl can be fatal.	A
Gender assignment is imminent and should be based on multi-disciplinary consensus taking into account the latest knowledge.	B
Do not delay surgical treatment in girls presenting with severe anomalies.	B
Offer more conservative approaches in less severe cases, in consultation with the parents.	B
Follow the recommendations for boys, for hypospadias repair and orchiopexy (from six months onwards and before two years of age).	A

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 [819-821]. Posterior urethral valves are found in 1 in 1,250 in a population undergoing foetal US screening [519]. An incidence of PUV of 1 in 5,000-12,500 live-births has been estimated [822, 823]. In one report, up to 46% of foetuses with a PUV diagnosis were terminated, indicating a possible decrease in incidence [824].

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) [825], the original classification by Hugh Hampton Young remains the most commonly used [826].

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' [826].

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' [826]. The transverse membrane described has been attributed to incomplete dissolution from the urogenital portion of the cloacal membrane [827]. The embryology of the urethral valves is poorly understood. The membrane may be an abnormal insertion of the mesonephric ducts into the foetal cloaca [828].

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 UUT. 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 hydroureteronephrosis and a distended bladder are suspicious signs of a urethral valve. Also a thick-walled bladder and a dilated posterior urethra ('keyhole' sign) make a PUV likely. In one study, however, the keyhole sign was not found to be a reliable predictor ($p = 0.27$) [829]. 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 [830]. 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 [831]. Other types of pop-off mechanism include bladder diverticula and urinary extravasation, with or without urinary ascites [832]. However, in the long-term, a supposed protective effect did not show a significant difference compared to other patients with PUV [833, 834].

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 [821]. Initial management includes a multi-disciplinary team involving a paediatric nephrologist.

3.17.4 ***Management***

3.17.4.1 Antenatal treatment

About 40-60% of PUV are discovered before birth [835]. 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 [836].

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% [836-838]. Although shunting is effective in reversing oligohydramnios, it makes no difference to the outcome and longterm results of patients with PUV [837, 838]. The PLUTO-trail (randomised study) could not prove a benefit of placing a shunt [839].

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 [840, 841].

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 were the urethra is too small to safely pass a small faetal 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 [842]. 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 [843].

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 [844]. 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 [845, 846].

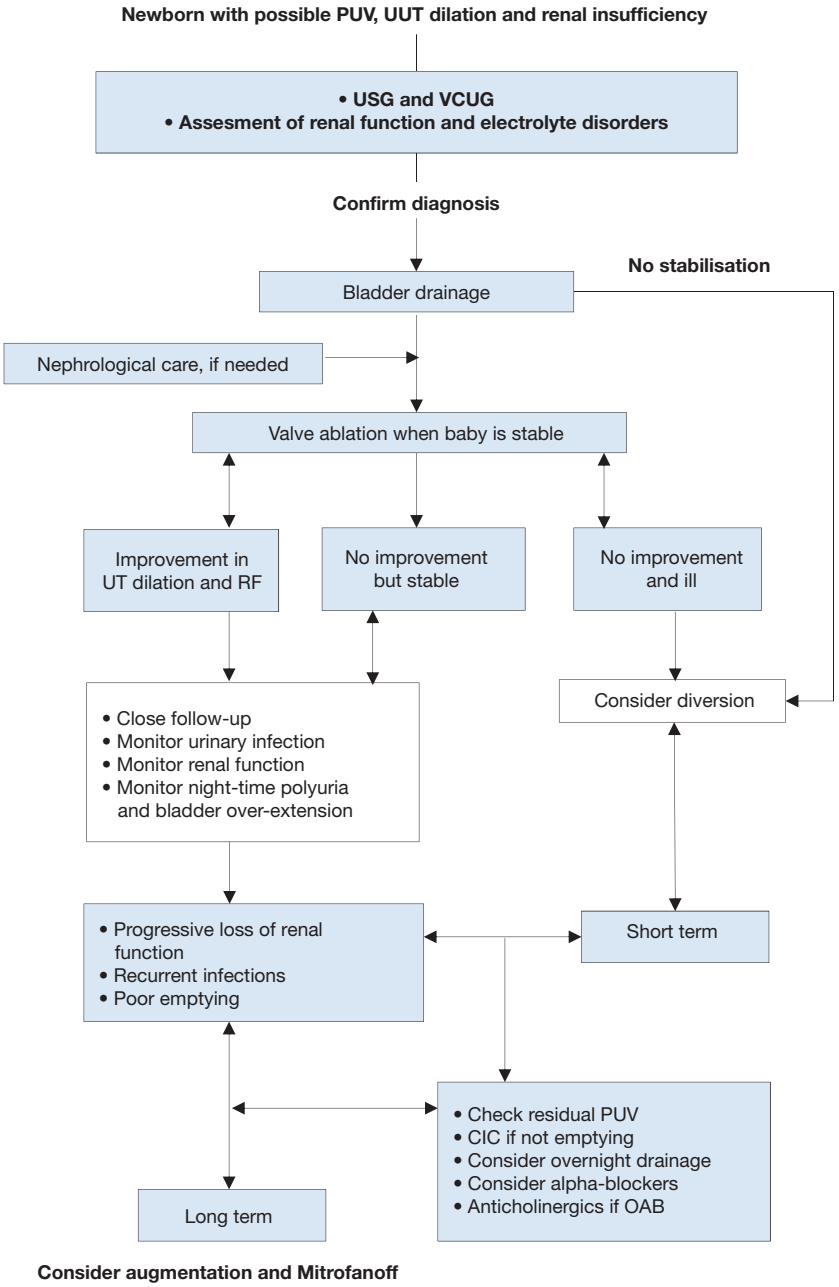
High diversion. If bladder drainage is insufficient to drain the UUT, high urinary diversion should be considered. Diversion may be suitable if there are recurrent infections of the upper tract, no improvement in renal function and/or an increase in upper tract dilatation, despite adequate bladder drainage. 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 [847-849]. 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% [850]. During the first months of life, antibiotic prophylaxis may be given especially in those with high-grade reflux [600] and in those with a phimosis, circumcision can be discussed in order to reduce the risk of UTIs [851]. 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 [819, 852]. 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 [853].

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 [821, 830]. 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) [854, 855]. In patients with poor bladder emptying α-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) [856] and in another study tamsulosin was effective [857]. Between 10% and 47% of patients may develop end-stage renal failure [819-821]. High creatinine nadir and severe bladder dysfunction are risk factors for renal replacement therapy [858]. Renal transplantation in these patients can be performed safely and effectively [859, 860]. Deterioration of the graft function is mainly related to LUTD [860, 861]. 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 run 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 hydroureteronephrosis 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 run between 10% and 47% of patients develop end-stage renal failure due to primary dysplasia and/or further deteroration because of bladder dysfunction.	2a
Renal transplantation in these patients is safe and effective, if the bladder function is normalised.	

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

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 [862]. In about 3% of children seen at paediatric hospital trauma centres, there is significant involvement of the genitourinary tract [863]. 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 [862].

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 [864].

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) [865].

Table 13: Renal injury classified according to the kidney injury scale of the American Association for the Surgery of Trauma [865]

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 [866].

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 [867]. 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 [868]. 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 [869]. 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 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 [870].

3.18.1.5 *Recommendations for the diagnosis and management of paediatric renal trauma*

Recommendations	GR
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.	B
Use rapid spiral computed tomography scanning for diagnostic and staging purposes.	B
Manage most injured kidneys conservatively.	B
Offer surgical intervention in case of haemodynamic instability and a Grade V renal injury.	A

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 [871]. 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 [871]. Diagnostic accuracy of CT scanning can be improved by performing a delayed CT scan up to ten minutes after injection of the contrast material [872]. 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 nephrostromy tube drainage of urinomas can be successful, as well as internal stenting of ureteral injuries [873].

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 [874].

3.18.2.3 *Recommendations for the diagnosis and management of paediatric ureteral trauma*

Recommendations	GR
Diagnose suspected ureteral injuries by retrograde pyelogram.	
However, in the initial phase of an injury, it is very likely that ureteral injuries will not be detected by routine imaging methods, including contrast-enhanced spiral computed tomography.	A
Manage ureteral injuries endoscopically, using internal stenting or drainage of a urinoma, either percutaneously or via a nephrostomy tube.	B
Manage distal and proximal ureteral injuries with open surgery.	B
Manage distal injuries with direct re-anastomosis and ureteroneocystostomy.	B
Manage proximal injuries, with transureteroureterostomy, ureteral replacement with bowel or appendix, or even autotransplantation.	B

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 [875].

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 [876].

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 [877].

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.

Intra-peritoneal 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 Intra-peritoneal injuries

The accepted management of intra-peritoneal 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 [878]. Usually, after about seven to ten days, a repeat cystogram is performed to ensure healing is taking place properly.

3.18.3.2.2 Extra-peritoneal injuries

Non-operative management with catheter drainage for seven to ten days alone is the method of choice for extra-peritoneal 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 [879].

3.18.3.3 Recommendations for the diagnosis and management of paediatric bladder injuries

Recommendations	GR
Use retrograde cystography to diagnose suspected bladder injuries.	
Ensure that the bladder has been filled to its full capacity and an additional film is taken after drainage.	A
Manage extra-peritoneal bladder ruptures conservatively with a transurethral catheter left in place for seven to ten days.	A
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.	A

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 [880].

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 [881].

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 [882]. 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% [883]. 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% [884]. Another study reported strictures and impotence in 67% of boys, although all the boys were continent [883].

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 [885].

3.18.4.3 Recommendations for the diagnosis and management of paediatric trauma

Recommendations	GR
Assess the urethra by retrograde urethrogram in case of suspected urethral trauma.	A
Perform a rectal examination to determine the position of the prostate.	B
Manage bulbous urethral injuries conservatively with a transurethral catheter.	B
Manage posterior urethral disruption by either: • primary reconstruction; • primary drainage with a suprapubic catheter alone and delayed repair; • primary re-alignment with a transurethral catheter.	C

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 [886]. As children are developing,

they have a high metabolic rate and low fat and nutrient stores, which means they are more susceptible to metabolic disturbances caused by surgical stress [887]. The metabolic response to anaesthesia and surgery in infants and children is related to the severity of the operation [888].

*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 [889, 890].

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 [891]. 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 [892].

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 [892].

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) [893]. Calculations have shown that anaesthetised and non-anaesthetised children have similar fluid requirements [894].

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 [895].

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 [896]. Berry (1986) proposed simplified guidelines for fluid administration according to the child's age and severity of surgical trauma [897] (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.* [896]			
Hour of fluid replacement	**Maintenance fluid**	**Fasting deficit replacement**	**Persistent losses**
First hour	As Table 14	50%	Third space + blood loss replacement
Second hour		25%	
Third hour		25%	
Berry [897]			
First hour	< 3 years: 25 mL/kg > 4 years: 15 mL/kg		Blood replacement 1:1 with blood or colloid **or** 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 **or** 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 [892].

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) [890].

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 [886, 895]. 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 [890].

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 [887], while remembering that withholding oral fluids post-operatively from children undergoing day surgery helps prevent vomiting [898]. 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 [899]. 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 [900].

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 [900, 901]. 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 [890, 900, 902-905]. 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 [890].

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% [898, 906, 907]. 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 [908]. 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 [909]. 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 [910]. The EAU Panel members 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 fluid management***

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	GR
Ensure that shorter pre-operative fasting periods apply for elective surgeries (up to four hours).	B
Use fluids with lower dextrose concentrations since hyperglycaemia is common in children, compared to intra-operative hypoglycaemia (which is very rare).	B
Do not routinely use hypotonic fluid in hospitalised children because they are at high risk of developing hyponatraemia.	A
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.	B
Start early oral fluid intake in patients scheduled for minor surgical procedures.	A

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 [917]. However, there is still no standardised algorithm for management of post-operative pain in children [918]. 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 [919].

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 [911, 920-923]. Many studies have indicated that deficient or insufficient analgesia may be the cause of future behavioural and

somatic sequelae [912, 924-926]. 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 [927, 928].

One of the most important topics in paediatric pain management is informing and involving the child and parents during this process. Parents and patients can manage post-operative pain at home or in hospital if provided with the correct information. Parents and patients, if they are old enough, can actively take part in pain management in patient-family-controlled analgesia applications [913, 929-933].

*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 [934]. 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 [930]. 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 [935]. 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 [936]. 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 [937]. Despite this, adequate pain management is still below expectation [938]. 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 [939-943].

Although DPNB and topical anaesthetics seem to have a similar post-operative analgesic effect, DPNB is still the most preferred method [944] (LE: 1a). Ultrasound guidance may improve the results, with an increase in procedural time [945, 946]. Caudal blockade methods have similar efficacy compared to DPNB. However, parents should be informed about the more frequent incidence of post-operative motor weakness and micturition problems [947-952].

3.20.3.3 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 [953-967]. Both single and combined use of these agents is effective [954, 955, 957, 958, 963, 965].

Penile blocks can be used for post-operative analgesia and have similar post-operative analgesic properties as caudal blocks [968]. Two penile blocks at the beginning and end of surgery seems to provide better pain relief [969]. 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 [392, 970-972] nerve block [973, 974], wound infiltration or instillation, and irrigation with local anaesthetics [975-977] have been shown to have adequate post-operative analgesic properties. Combinations may improve the results [978].

Table 17: List of several drugs used in post-operative pain management in children [911-916]

Name	Route of administration	Dose	Side effects	General remarks	Caution
Non-narcotics					
Acetaminophen	Rectal Oral Intravenous	40 mg/kg loading, 20 mg/kg/dose 4 times/day 15-40 mg/kg, followed by 30 mg/kg/8 h Propacetamol (prodrug)	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
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, dipyrone	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
Narcotics					
Opioids			Nausea, vomiting, dyspepsia, constipation, urinary retention, respiratory depression, drowsiness, euphoria		
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, 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		
Regional (local) anaesthetics					
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		

3.20.3.4 Bladder and kidney surgery

Continuous epidural infusion of local anaesthetics [979-981], as well as systemic (intravenous) application of analgesics [982], 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 [971, 983-986].

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 [987].

Caudal blocks plus systemic analgesics [988], and continuous epidural analgesia, are effective in terms of decreased post-operative morphine requirement after renal surgery [989, 990]. However, when there is a relative contraindication to line insertion, a less experienced anaesthetist is available, or parents prefer it [991], 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 [992]. For laparoscopic approaches, intra-peritoneal spraying of local anaesthetic before incision of the perirenal fascia may be beneficial [993].

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 lombotomy)			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	GR
Prevent/treat pain in children of all ages.	B
Evaluate pain using age-compatible assessment tools.	B
Inform patients and parents accurately.	B
Use pre-emptive and balanced analgesia in order to decrease the side effects of opioids.	B

4. REFERENCES

1. Stein, R., *et al.* Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol, 2015. 67: 546. https://www.ncbi.nlm.nih.gov/pubmed/25477258
2. Tekgul, S., *et al.* EAU guidelines on vesicoureteral reflux in children. Eur Urol, 2012. 62: 534. https://www.ncbi.nlm.nih.gov/pubmed/22698573
3. Radmayr, C., *et al.* Management of undescended testes: European Association of Urology/European Society for Paediatric Urology Guidelines. J Pediatr Urol, 2016. https://www.ncbi.nlm.nih.gov/pubmed/27687532
4. Silay, M.S., *et al.* The role of antibiotic prophylaxis in antenatal hydronephrosis: A systematic review. J Ped Urol, 2017. prior to print

5. Phillips, B., *et al.* Oxford Centre for Evidence-Based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998. 2014. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
6. Gairdner, D. The fate of the foreskin, a study of circumcision. Br Med J, 1949. 2: 1433. https://www.ncbi.nlm.nih.gov/pubmed/15408299
7. Kuehhas, F.E., *et al.* Incidence of balanitis xerotica obliterans in boys younger than 10 years presenting with phimosis. Urol Int, 2013. 90: 439. https://www.ncbi.nlm.nih.gov/pubmed/23296396
8. Oster, J. Further fate of the foreskin. Incidence of preputial adhesions, phimosis, and smegma among Danish schoolboys. Arch Dis Child, 1968. 43: 200. https://www.ncbi.nlm.nih.gov/pubmed/5689532
9. Chu, C.C., *et al.* Topical steroid treatment of phimosis in boys. J Urol, 1999. 162: 861. https://www.ncbi.nlm.nih.gov/pubmed/10458396
10. Elmore, J.M., *et al.* Topical steroid therapy as an alternative to circumcision for phimosis in boys younger than 3 years. J Urol, 2002. 168: 1746. https://www.ncbi.nlm.nih.gov/pubmed/12352350
11. ter Meulen, P.H., *et al.* A conservative treatment of phimosis in boys. Eur Urol, 2001. 40: 196. https://www.ncbi.nlm.nih.gov/pubmed/11528198
12. Zavras, N., *et al.* Conservative treatment of phimosis with fluticasone proprionate 0.05%: a clinical study in 1185 boys. J Pediatr Urol, 2009. 5: 181. https://www.ncbi.nlm.nih.gov/pubmed/19097823
13. Reddy, S., *et al.* Local steroid therapy as the first-line treatment for boys with symptomatic phimosis - a long-term prospective study. Acta Paediatr, 2012. 101: e130. https://www.ncbi.nlm.nih.gov/pubmed/22103624
14. Golubovic, Z., *et al.* The conservative treatment of phimosis in boys. Br J Urol, 1996. 78: 786. https://www.ncbi.nlm.nih.gov/pubmed/8976781
15. Pileggi, F.O., *et al.* Is suppression of hypothalamic-pituitary-adrenal axis significant during clinical treatment of phimosis? J Urol, 2010. 183: 2327. https://www.ncbi.nlm.nih.gov/pubmed/20400146
16. Wu, X., *et al.* A report of 918 cases of circumcision with the Shang Ring: comparison between children and adults. Urology, 2013. 81: 1058. https://www.ncbi.nlm.nih.gov/pubmed/23465168
17. Miernik, A., *et al.* Complete removal of the foreskin--why? Urol Int, 2011. 86: 383. https://www.ncbi.nlm.nih.gov/pubmed/21474914
18. Herndon, C.D., *et al.* A multicenter outcomes analysis of patients with neonatal reflux presenting with prenatal hydronephrosis. J Urol, 1999. 162: 1203. https://www.ncbi.nlm.nih.gov/pubmed/10458467
19. Hiraoka, M., *et al.* Meatus tightly covered by the prepuce is associated with urinary infection. Pediatr Int, 2002. 44: 658. https://www.ncbi.nlm.nih.gov/pubmed/12421265
20. To, T., *et al.* Cohort study on circumcision of newborn boys and subsequent risk of urinary-tract infection. Lancet, 1998. 352: 1813. https://www.ncbi.nlm.nih.gov/pubmed/9851381
21. Wiswell, T.E. The prepuce, urinary tract infections, and the consequences. Pediatrics, 2000. 105: 860. https://www.ncbi.nlm.nih.gov/pubmed/10742334
22. Ladenhauf, H.N., *et al.* Reduced bacterial colonisation of the glans penis after male circumcision in children--a prospective study. J Pediatr Urol, 2013. 9: 1137. https://www.ncbi.nlm.nih.gov/pubmed/23685114
23. Larke, N.L., *et al.* Male circumcision and penile cancer: a systematic review and meta-analysis. Cancer Causes Control, 2011. 22: 1097. https://www.ncbi.nlm.nih.gov/pubmed/21695385
24. American Academy of Pediatrics: Report of the Task Force on Circumcision. Pediatrics, 1989. 84: 388. https://www.ncbi.nlm.nih.gov/pubmed/2664697
25. Thompson, H.C., *et al.* Report of the ad hoc task force on circumcision. Pediatrics, 1975. 56: 610. https://www.ncbi.nlm.nih.gov/pubmed/1174384
26. Elalfy, M.S., *et al.* Risk of bleeding and inhibitor development after circumcision of previously untreated or minimally treated severe hemophilia A children. Pediatr Hematol Oncol, 2012. 29: 485. https://www.ncbi.nlm.nih.gov/pubmed/22866674

27. Karaman, M.I., *et al.* Circumcision in bleeding disorders: improvement of our cost effective method with diathermic knife. Urol J, 2014. 11: 1406.
https://www.ncbi.nlm.nih.gov/pubmed/24807751
28. Christakis, D.A., *et al.* A trade-off analysis of routine newborn circumcision. Pediatrics, 2000. 105: 246.
https://www.ncbi.nlm.nih.gov/pubmed/10617731
29. Griffiths, D.M., *et al.* A prospective survey of the indications and morbidity of circumcision in children. Eur Urol, 1985. 11: 184.
https://www.ncbi.nlm.nih.gov/pubmed/4029234
30. Morris, B.J., *et al.* A 'snip' in time: what is the best age to circumcise? BMC Pediatr, 2012. 12: 20.
https://www.ncbi.nlm.nih.gov/pubmed/22373281
31. Ross, J.H., Circumcision: Pro and con., in Pediatric urology for the general urologist., J.S. Elder, Editor. 1996, Igaku-Shoin: New York.
32. Weiss, H.A., *et al.* Complications of circumcision in male neonates, infants and children: a systematic review. BMC Urol, 2010. 10: 2.
https://www.ncbi.nlm.nih.gov/pubmed/20158883
33. Anand, A., *et al.* Mannitol for paraphimosis reduction. Urol Int, 2013. 90: 106.
https://www.ncbi.nlm.nih.gov/pubmed/23257575
34. DeVries, C.R., *et al.* Reduction of paraphimosis with hyaluronidase. Urology, 1996. 48: 464.
https://www.ncbi.nlm.nih.gov/pubmed/8804504
35. Sijstermans, K., *et al.* The frequency of undescended testis from birth to adulthood: a review. Int J Androl, 2008. 31: 1.
https://www.ncbi.nlm.nih.gov/pubmed/17488243
36. Berkowitz, G.S., *et al.* Prevalence and natural history of cryptorchidism. Pediatrics, 1993. 92: 44.
https://www.ncbi.nlm.nih.gov/pubmed/8100060
37. Kaefer, M., *et al.* The incidence of intersexuality in children with cryptorchidism and hypospadias: stratification based on gonadal palpability and meatal position. J Urol, 1999. 162: 1003.
https://www.ncbi.nlm.nih.gov/pubmed/10458421
38. Kollin, C., *et al.* Cryptorchidism: a clinical perspective. Pediatr Endocrinol Rev, 2014. 11 Suppl 2: 240.
https://www.ncbi.nlm.nih.gov/pubmed/24683948
39. Caesar, R.E., *et al.* The incidence of the cremasteric reflex in normal boys. J Urol, 1994. 152: 779.
https://www.ncbi.nlm.nih.gov/pubmed/7912745
40. Barthold, J.S., *et al.* The epidemiology of congenital cryptorchidism, testicular ascent and orchiopexy. J Urol, 2003. 170: 2396.
https://www.ncbi.nlm.nih.gov/pubmed/14634436
41. Turek, P.J., *et al.* The absent cryptorchid testis: surgical findings and their implications for diagnosis and etiology. J Urol, 1994. 151: 718.
https://www.ncbi.nlm.nih.gov/pubmed/7905931
42. Rabinowitz, R., *et al.* Late presentation of cryptorchidism: the etiology of testicular re-ascent. J Urol, 1997. 157: 1892.
https://www.ncbi.nlm.nih.gov/pubmed/9112557
43. Cendron, M., *et al.* Anatomical, morphological and volumetric analysis: a review of 759 cases of testicular maldescent. J Urol, 1993. 149: 570.
https://www.ncbi.nlm.nih.gov/pubmed/8094761
44. Braga, L.H., *et al.* Is there an optimal contralateral testicular cut-off size that predicts monorchism in boys with nonpalpable testicles? J Pediatr Urol, 2014. 10: 693.
https://www.ncbi.nlm.nih.gov/pubmed/25008806
45. Hurwitz, R.S., *et al.* How well does contralateral testis hypertrophy predict the absence of the nonpalpable testis? J Urol, 2001. 165: 588.
https://www.ncbi.nlm.nih.gov/pubmed/11176443
46. Elert, A., *et al.* Population-based investigation of familial undescended testis and its association with other urogenital anomalies. J Pediatr Urol, 2005. 1: 403.
https://www.ncbi.nlm.nih.gov/pubmed/18947580
47. Hrebinko, R.L., *et al.* The limited role of imaging techniques in managing children with undescended testes. J Urol, 1993. 150: 458.
https://www.ncbi.nlm.nih.gov/pubmed/8100860
48. Tasian, G.E., *et al.* Diagnostic performance of ultrasound in nonpalpable cryptorchidism: a systematic review and meta-analysis. Pediatrics, 2011. 127: 119.
https://www.ncbi.nlm.nih.gov/pubmed/21149435

49. Elder, J.S. Ultrasonography is unnecessary in evaluating boys with a nonpalpable testis. Pediatrics, 2002. 110: 748.
https://www.ncbi.nlm.nih.gov/pubmed/12359789
50. Tasian, G.E., *et al.* Diagnostic imaging in cryptorchidism: utility, indications, and effectiveness. J Pediatr Surg, 2011. 46: 2406.
https://www.ncbi.nlm.nih.gov/pubmed/22152893
51. Wenzler, D.L., *et al.* What is the rate of spontaneous testicular descent in infants with cryptorchidism? J Urol, 2004. 171: 849.
https://www.ncbi.nlm.nih.gov/pubmed/14713841
52. Park, K.H., *et al.* Histological evidences suggest recommending orchiopexy within the first year of life for children with unilateral inguinal cryptorchid testis. Int J Urol, 2007. 14: 616.
https://www.ncbi.nlm.nih.gov/pubmed/17645605
53. Engeler, D.S., *et al.* Early orchiopexy: prepubertal intratubular germ cell neoplasia and fertility outcome. Urology, 2000. 56: 144.
https://www.ncbi.nlm.nih.gov/pubmed/10869645
54. Rajfer, J., *et al.* Hormonal therapy of cryptorchidism. A randomized, double-blind study comparing human chorionic gonadotropin and gonadotropin-releasing hormone. N Engl J Med, 1986. 314: 466.
https://www.ncbi.nlm.nih.gov/pubmed/2868413
55. Forest, M.G., *et al.* Undescended testis: comparison of two protocols of treatment with human chorionic gonadotropin. Effect on testicular descent and hormonal response. Horm Res, 1988. 30: 198.
https://www.ncbi.nlm.nih.gov/pubmed/2907898
56. Pyorala, S., *et al.* A review and meta-analysis of hormonal treatment of cryptorchidism. J Clin Endocrinol Metab, 1995. 80: 2795.
https://www.ncbi.nlm.nih.gov/pubmed/7673426
57. Lala, R., *et al.* Combined therapy with LHRH and HCG in cryptorchid infants. Eur J Pediatr, 1993. 152 Suppl 2: S31.
https://www.ncbi.nlm.nih.gov/pubmed/8101810
58. Forest, M.G., *et al.* Effects of human chorionic gonadotropin, androgens, adrenocorticotropin hormone, dexamethasone and hyperprolactinemia on plasma sex steroid-binding protein. Ann N Y Acad Sci, 1988. 538: 214.
https://www.ncbi.nlm.nih.gov/pubmed/2847619
59. Aycan, Z., *et al.* Evaluation of low-dose hCG treatment for cryptorchidism. Turk J Pediatr, 2006. 48: 228.
https://www.ncbi.nlm.nih.gov/pubmed/17172066
60. Hesse, V., *et al.* Three injections of human chorionic gonadotropin are as effective as ten injections in the treatment of cryptorchidism. Horm Res, 1988. 30: 193.
https://www.ncbi.nlm.nih.gov/pubmed/2907897
61. Hagberg, S., *et al.* Treatment of undescended testes with intranasal application of synthetic LH-RH. Eur J Pediatr, 1982. 139: 285.
https://www.ncbi.nlm.nih.gov/pubmed/6133757
62. Hadziselimovic, F., *et al.* Long-term effect of luteinizing hormone-releasing hormone analogue (buserelin) on cryptorchid testes. J Urol, 1987. 138: 1043.
https://www.ncbi.nlm.nih.gov/pubmed/9258170
63. Schwentner, C., *et al.* Neoadjuvant gonadotropin-releasing hormone therapy before surgery may improve the fertility index in undescended testes: a prospective randomized trial. J Urol, 2005. 173: 974.
https://www.ncbi.nlm.nih.gov/pubmed/16600785
64. Hadziselimovic, F., *et al.* Treatment with a luteinizing hormone-releasing hormone analogue after successful orchiopexy markedly improves the chance of fertility later in life. J Urol, 1997. 158: 1193.
https://www.ncbi.nlm.nih.gov/pubmed/2888905
65. Cortes, D., *et al.* Hormonal treatment may harm the germ cells in 1 to 3-year-old boys with cryptorchidism. J Urol, 2000. 163: 1290.
https://www.ncbi.nlm.nih.gov/pubmed/10737531
66. Ritzen, E.M. Undescended testes: a consensus on management. Eur J Endocrinol, 2008. 159 Suppl 1: S87.
https://www.ncbi.nlm.nih.gov/pubmed/18728121
67. Kollin, C., *et al.* Surgical treatment of unilaterally undescended testes: testicular growth after randomization to orchiopexy at age 9 months or 3 years. J Urol, 2007. 178: 1589.
https://www.ncbi.nlm.nih.gov/pubmed/17707045

68. Novaes, H.F., *et al.* Single scrotal incision orchiopexy - a systematic review. Int Braz J Urol, 2013. 39: 305.
https://www.ncbi.nlm.nih.gov/pubmed/23849581
69. Docimo, S.G. The results of surgical therapy for cryptorchidism: a literature review and analysis. J Urol, 1995. 154: 1148.
https://www.ncbi.nlm.nih.gov/pubmed/7637073
70. Ziylan, O., *et al.* Failed orchiopexy. Urol Int, 2004. 73: 313.
https://www.ncbi.nlm.nih.gov/pubmed/15604574
71. Prentiss, R.J., *et al.* Undescended testis: surgical anatomy of spermatic vessels, spermatic surgical triangles and lateral spermatic ligament. J Urol, 1960. 83: 686.
https://www.ncbi.nlm.nih.gov/pubmed/14434738
72. Kozminski, D.J., *et al.* Orchiopexy without Transparenchymal Fixation Suturing: A 29-Year Experience. J Urol, 2015. 194: 1743.
https://www.ncbi.nlm.nih.gov/pubmed/26141850
73. Martin, J.M., *et al.* Is radiotherapy a good adjuvant strategy for men with a history of cryptorchism and stage I seminoma? Int J Radiat Oncol Biol Phys, 2010. 76: 65.
https://www.ncbi.nlm.nih.gov/pubmed/19362785
74. Na, S.W., *et al.* Single scrotal incision orchiopexy for children with palpable low-lying undescended testis: early outcome of a prospective randomized controlled study. Korean J Urol, 2011. 52: 637.
https://www.ncbi.nlm.nih.gov/pubmed/22025961
75. Parsons, J.K., *et al.* The low scrotal approach to the ectopic or ascended testicle: prevalence of a patent processus vaginalis. J Urol, 2003. 169: 1832.
https://www.ncbi.nlm.nih.gov/pubmed/12686856
76. Wayne, C., *et al.* What is the ideal surgical approach for intra-abdominal testes? A systematic review. Pediatr Surg Int, 2015. 31: 327.
https://www.ncbi.nlm.nih.gov/pubmed/25663531
77. Cortesi, N., *et al.* Diagnosis of bilateral abdominal cryptorchidism by laparoscopy. Endoscopy, 1976. 8: 33.
https://www.ncbi.nlm.nih.gov/pubmed/16743
78. Jordan, G.H., *et al.* Laparoscopic single stage and staged orchiopexy. J Urol, 1994. 152: 1249.
https://www.ncbi.nlm.nih.gov/pubmed/7915336
79. Chandrasekharam, V.V. Laparoscopy vs inguinal exploration for nonpalpable undescended testis. Indian J Pediatr, 2005. 72: 1021.
https://www.ncbi.nlm.nih.gov/pubmed/16388149
80. Snodgrass, W.T., *et al.* Scrotal exploration for unilateral nonpalpable testis. J Urol, 2007. 178: 1718.
https://www.ncbi.nlm.nih.gov/pubmed/17707015
81. Cisek, L.J., *et al.* Current findings in diagnostic laparoscopic evaluation of the nonpalpable testis. J Urol, 1998. 160: 1145.
https://www.ncbi.nlm.nih.gov/pubmed/9719296
82. Patil, K.K., *et al.* Laparoscopy for impalpable testes. BJU Int, 2005. 95: 704.
https://www.ncbi.nlm.nih.gov/pubmed/15784081
83. Elderwy, A.A., *et al.* Laparoscopic versus open orchiopexy in the management of peeping testis: a multi-institutional prospective randomized study. J Pediatr Urol, 2014. 10: 605.
https://www.ncbi.nlm.nih.gov/pubmed/25042877
84. Kirsch, A.J., *et al.* Surgical management of the nonpalpable testis: the Children's Hospital of Philadelphia experience. J Urol, 1998. 159: 1340.
https://www.ncbi.nlm.nih.gov/pubmed/9507881
85. Fowler, R., *et al.* The role of testicular vascular anatomy in the salvage of high undescended testes. Aust N Z J Surg, 1959. 29: 92.
https://www.ncbi.nlm.nih.gov/pubmed/13849840
86. Koff, S.A., *et al.* Treatment of high undescended testes by low spermatic vessel ligation: an alternative to the Fowler-Stephens technique. J Urol, 1996. 156: 799.
https://www.ncbi.nlm.nih.gov/pubmed/8683787
87. Esposito, C., *et al.* Exploration of inguinal canal is mandatory in cases of non palpable testis if laparoscopy shows elements entering a closed inguinal ring. Eur J Pediatr Surg, 2010. 20: 138.
https://www.ncbi.nlm.nih.gov/pubmed/19746341
88. Radmayr, C., *et al.* Long-term outcome of laparoscopically managed nonpalpable testes. J Urol, 2003. 170: 2409.
https://www.ncbi.nlm.nih.gov/pubmed/14634439

89. Baker, L.A., *et al.* A multi-institutional analysis of laparoscopic orchidopexy. BJU Int, 2001. 87: 484. https://www.ncbi.nlm.nih.gov/pubmed/11298039
90. Dave, S., *et al.* Open versus laparoscopic staged Fowler-Stephens orchiopexy: impact of long loop vas. J Urol, 2009. 182: 2435. https://www.ncbi.nlm.nih.gov/pubmed/19765743
91. Wacksman, J., *et al.* Laparoscopically assisted testicular autotransplantation for management of the intraabdominal undescended testis. J Urol, 1996. 156: 772. https://www.ncbi.nlm.nih.gov/pubmed/8683780
92. Penson, D., *et al.* Effectiveness of hormonal and surgical therapies for cryptorchidism: a systematic review. Pediatrics, 2013. 131: e1897. https://www.ncbi.nlm.nih.gov/pubmed/23690511
93. Koni, A., *et al.* Histopathological evaluation of orchiectomy specimens in 51 late postpubertal men with unilateral cryptorchidism. J Urol, 2014. 192: 1183. https://www.ncbi.nlm.nih.gov/pubmed/24840535
94. Trussell, J.C., *et al.* The relationship of cryptorchidism to fertility. Curr Urol Rep, 2004. 5: 142. https://www.ncbi.nlm.nih.gov/pubmed/15028208
95. Hadziselimovic, F., *et al.* The importance of both an early orchidopexy and germ cell maturation for fertility. Lancet, 2001. 358: 1156. https://www.ncbi.nlm.nih.gov/pubmed/11597673
96. Lee, P.A. Fertility after cryptorchidism: epidemiology and other outcome studies. Urology, 2005. 66: 427. https://www.ncbi.nlm.nih.gov/pubmed/16098371
97. Chua, M.E., *et al.* Hormonal therapy using gonadotropin releasing hormone for improvement of fertility index among children with cryptorchidism: a meta-analysis and systematic review. J Pediatr Surg, 2014. 49: 1659. https://www.ncbi.nlm.nih.gov/pubmed/25475814
98. Coughlin, M.T., *et al.* Age at unilateral orchiopexy: effect on hormone levels and sperm count in adulthood. J Urol, 1999. 162: 986. https://www.ncbi.nlm.nih.gov/pubmed/10458417
99. Tasian, G.E., *et al.* Age at orchiopexy and testis palpability predict germ and Leydig cell loss: clinical predictors of adverse histological features of cryptorchidism. J Urol, 2009. 182: 704. https://www.ncbi.nlm.nih.gov/pubmed/19539332
100. Dieckmann, K.P., *et al.* Clinical epidemiology of testicular germ cell tumors. World J Urol, 2004. 22: 2. https://www.ncbi.nlm.nih.gov/pubmed/15034740
101. Pettersson, A., *et al.* Age at surgery for undescended testis and risk of testicular cancer. N Engl J Med, 2007. 356: 1835. https://www.ncbi.nlm.nih.gov/pubmed/17476009
102. Walsh, T.J., *et al.* Prepubertal orchiopexy for cryptorchidism may be associated with lower risk of testicular cancer. J Urol, 2007. 178: 1440. https://www.ncbi.nlm.nih.gov/pubmed/17706709
103. Kapur, P., *et al.* Pediatric hernias and hydroceles. Pediatr Clin North Am, 1998. 45: 773. https://www.ncbi.nlm.nih.gov/pubmed/9728185
104. Barthold, J.S., Abnormalities of the testis and scrotum and their surgical management, in Campbell-Walsh Urology, A.J. Wein & e. al., Eds. 2012, Elsevier Saunders: Philadelphia.
105. Schneck, F.X., *et al.*, Abnormalities of the testes and scrotum and their surgical management in Campbell's Urology, 2002, WB Saunders: Philadelphia.
106. Rubenstein, R.A., *et al.* Benign intrascrotal lesions. J Urol, 2004. 171: 1765. https://www.ncbi.nlm.nih.gov/pubmed/15076274
107. Lin, H.C., *et al.* Testicular teratoma presenting as a transilluminating scrotal mass. Urology, 2006. 67: 1290.e3. https://www.ncbi.nlm.nih.gov/pubmed/16750249
108. Skoog, S.J. Benign and malignant pediatric scrotal masses. Pediatr Clin North Am, 1997. 44: 1229. https://www.ncbi.nlm.nih.gov/pubmed/9326960
109. Koski, M.E., *et al.* Infant communicating hydroceles--do they need immediate repair or might some clinically resolve? J Pediatr Surg, 2010. 45: 590. https://www.ncbi.nlm.nih.gov/pubmed/20223325
110. Stringer, M.D., *et al.*, Patent processus vaginalis., in Pediatric urology, 2001, WB Saunders: Philadelphia.

111. Stylianos, S., *et al.* Incarceration of inguinal hernia in infants prior to elective repair. J Pediatr Surg, 1993. 28: 582.
https://www.ncbi.nlm.nih.gov/pubmed/8483072
112. Hall, N.J., *et al.* Surgery for hydrocele in children-an avoidable excess? J Pediatr Surg, 2011. 46: 2401.
https://www.ncbi.nlm.nih.gov/pubmed/22152892
113. Saad, S., *et al.* Ten-year review of groin laparoscopy in 1001 pediatric patients with clinical unilateral inguinal hernia: an improved technique with transhernia multiple-channel scope. J Pediatr Surg, 2011. 46: 1011.
https://www.ncbi.nlm.nih.gov/pubmed/21616272
114. Christensen, T., *et al.* New onset of hydroceles in boys over 1 year of age. Int J Urol, 2006. 13: 1425.
https://www.ncbi.nlm.nih.gov/pubmed/17083397
115. Cavusoglu, Y.H., *et al.* Acute scrotum -- etiology and management. Indian J Pediatr, 2005. 72: 201.
https://www.ncbi.nlm.nih.gov/pubmed/15812112
116. Klin, B., *et al.* Epididymitis in childhood: a clinical retrospective study over 5 years. Isr Med Assoc J, 2001. 3: 833.
https://www.ncbi.nlm.nih.gov/pubmed/11729579
117. Makela, E., *et al.* A 19-year review of paediatric patients with acute scrotum. Scand J Surg, 2007. 96: 62.
https://www.ncbi.nlm.nih.gov/pubmed/17461315
118. McAndrew, H.F., *et al.* The incidence and investigation of acute scrotal problems in children. Pediatr Surg Int, 2002. 18: 435.
https://www.ncbi.nlm.nih.gov/pubmed/12415374
119. Sakellaris, G.S., *et al.* Acute epididymitis in Greek children: a 3-year retrospective study. Eur J Pediatr, 2008. 167: 765.
https://www.ncbi.nlm.nih.gov/pubmed/17786475
120. Varga, J., *et al.* Acute scrotal pain in children--ten years' experience. Urol Int, 2007. 78: 73.
https://www.ncbi.nlm.nih.gov/pubmed/17192737
121. Bingol-Kologlu, M., *et al.* An exceptional complication following appendectomy: acute inguinal and scrotal suppuration. Int Urol Nephrol, 2006. 38: 663.
https://www.ncbi.nlm.nih.gov/pubmed/17160451
122. Dayanir, Y.O., *et al.* Epididymoorchitis mimicking testicular torsion in Henoch-Schonlein purpura. Eur Radiol, 2001. 11: 2267.
https://www.ncbi.nlm.nih.gov/pubmed/11702171
123. Diamond, D.A., *et al.* Neonatal scrotal haematoma: mimicker of neonatal testicular torsion. BJU Int, 2003. 91: 675.
https://www.ncbi.nlm.nih.gov/pubmed/12699483
124. Ha, T.S., *et al.* Scrotal involvement in childhood Henoch-Schonlein purpura. Acta Paediatr, 2007. 96: 552.
https://www.ncbi.nlm.nih.gov/pubmed/17306010
125. Hara, Y., *et al.* Acute scrotum caused by Henoch-Schonlein purpura. Int J Urol, 2004. 11: 578.
https://www.ncbi.nlm.nih.gov/pubmed/15242376
126. Klin, B., *et al.* Acute idiopathic scrotal edema in children--revisited. J Pediatr Surg, 2002. 37: 1200.
https://www.ncbi.nlm.nih.gov/pubmed/12149702
127. Krause, W. Is acute idiopathic scrotal edema in children a special feature of neutrophilic eccrine hidradenitis? Dermatology, 2004. 208: 86; author reply 86.
https://www.ncbi.nlm.nih.gov/pubmed/14730248
128. Matsumoto, A., *et al.* Torsion of the hernia sac within a hydrocele of the scrotum in a child. Int J Urol, 2004. 11: 789.
https://www.ncbi.nlm.nih.gov/pubmed/15379947
129. Myers, J.B., *et al.* Torsion of an indirect hernia sac causing acute scrotum. J Pediatr Surg, 2004. 39: 122.
https://www.ncbi.nlm.nih.gov/pubmed/14694389
130. Ng, K.H., *et al.* An unusual presentation of acute scrotum after appendicitis. Singapore Med J, 2002. 43: 365.
https://www.ncbi.nlm.nih.gov/pubmed/12437045
131. Singh, S., *et al.* Acute scrotum in children: a rare presentation of acute, non-perforated appendicitis. Pediatr Surg Int, 2003. 19: 298.
https://www.ncbi.nlm.nih.gov/pubmed/12682749

132. van Langen, A.M., *et al.* Acute idiopathic scrotal oedema: four cases and a short review. Eur J Pediatr, 2001. 160: 455.
https://www.ncbi.nlm.nih.gov/pubmed/11475590
133. Vlazakis, S., *et al.* Right acute hemiscrotum caused by insertion of an inflamed appendix. BJU Int, 2002. 89: 967.
https://www.ncbi.nlm.nih.gov/pubmed/12010250
134. D'Andrea, A., *et al.* US in the assessment of acute scrotum. Crit Ultrasound J, 2013. 5: S8.
http://www.criticalultrasoundjournal.com/content/5/S1/S8
135. Davis, J.E., *et al.* Scrotal emergencies. Emerg Med Clin North Am, 2011. 29: 469.
https://www.ncbi.nlm.nih.gov/pubmed/21782069
136. Jimoh, B.M., *et al.* Idiopathic scrotal hematoma in neonate: a case report and review of the literature. Case Rep Urol, 2014. 2014: 212914.
https://www.ncbi.nlm.nih.gov/pubmed/24982811
137. Matzek, B.A., *et al.* Traumatic testicular dislocation after minor trauma in a pediatric patient. J Emerg Med, 2013. 45: 537.
https://www.ncbi.nlm.nih.gov/pubmed/23899815
138. Wright, S., *et al.* Emergency ultrasound of acute scrotal pain. Eur J Emerg Med, 2015. 22: 2.
https://www.ncbi.nlm.nih.gov/pubmed/24910960
139. Yusuf, G.T., *et al.* A review of ultrasound imaging in scrotal emergencies. J Ultrasound, 2013. 16: 171.
https://www.ncbi.nlm.nih.gov/pubmed/24432171
140. Remer, E.M., *et al.* ACR Appropriateness Criteria (R) acute onset of scrotal pain--without trauma, without antecedent mass. Ultrasound Q, 2012. 28: 47.
https://www.ncbi.nlm.nih.gov/pubmed/22357246
141. Kadish, H.A., *et al.* A retrospective review of pediatric patients with epididymitis, testicular torsion, and torsion of testicular appendages. Pediatrics, 1998. 102: 73.
https://www.ncbi.nlm.nih.gov/pubmed/9651416
142. Sauvat, F., *et al.* [Age for testicular torsion?]. Arch Pediatr, 2002. 9: 1226.
https://www.ncbi.nlm.nih.gov/pubmed/12536102
143. Somekh, E., *et al.* Acute epididymitis in boys: evidence of a post-infectious etiology. J Urol, 2004. 171: 391.
https://www.ncbi.nlm.nih.gov/pubmed/14665940
144. Yerkes, E.B., *et al.* Management of perinatal torsion: today, tomorrow or never? J Urol, 2005. 174: 1579.
https://www.ncbi.nlm.nih.gov/pubmed/16148656
145. Boettcher, M., *et al.* Clinical and sonographic features predict testicular torsion in children: a prospective study. BJU Int, 2013. 112: 1201.
https://www.ncbi.nlm.nih.gov/pubmed/23826981
146. Nelson, C.P., *et al.* The cremasteric reflex: a useful but imperfect sign in testicular torsion. J Pediatr Surg, 2003. 38: 1248.
https://www.ncbi.nlm.nih.gov/pubmed/23826981
147. Mushtaq, I., *et al.* Retrospective review of paediatric patients with acute scrotum. ANZ J Surg, 2003. 73: 55.
https://www.ncbi.nlm.nih.gov/pubmed/12534742
148. Murphy, F.L., *et al.* Early scrotal exploration in all cases is the investigation and intervention of choice in the acute paediatric scrotum. Pediatr Surg Int, 2006. 22: 413.
https://www.ncbi.nlm.nih.gov/pubmed/16602024
149. Baker, L.A., *et al.* An analysis of clinical outcomes using color doppler testicular ultrasound for testicular torsion. Pediatrics, 2000. 105: 604.
https://www.ncbi.nlm.nih.gov/pubmed/10699116
150. Gunther, P., *et al.* Acute testicular torsion in children: the role of sonography in the diagnostic workup. Eur Radiol, 2006. 16: 2527.
https://www.ncbi.nlm.nih.gov/pubmed/16724203
151. Kalfa, N., *et al.* Multicenter assessment of ultrasound of the spermatic cord in children with acute scrotum. J Urol, 2007. 177: 297.
https://www.ncbi.nlm.nih.gov/pubmed/17162068
152. Karmazyn, B., *et al.* Clinical and sonographic criteria of acute scrotum in children: a retrospective study of 172 boys. Pediatr Radiol, 2005. 35: 302.
https://www.ncbi.nlm.nih.gov/pubmed/15503003

153. Lam, W.W., *et al.* Colour Doppler ultrasonography replacing surgical exploration for acute scrotum: myth or reality? Pediatr Radiol, 2005. 35: 597.
https://www.ncbi.nlm.nih.gov/pubmed/15761770
154. Schalamon, J., *et al.* Management of acute scrotum in children--the impact of Doppler ultrasound. J Pediatr Surg, 2006. 41: 1377.
https://www.ncbi.nlm.nih.gov/pubmed/16863840
155. Pepe, P., *et al.* Does color Doppler sonography improve the clinical assessment of patients with acute scrotum? Eur J Radiol, 2006. 60: 120.
https://www.ncbi.nlm.nih.gov/pubmed/16730939
156. Kalfa, N., *et al.* Ultrasonography of the spermatic cord in children with testicular torsion: impact on the surgical strategy. J Urol, 2004. 172: 1692.
https://www.ncbi.nlm.nih.gov/pubmed/15371792
157. Nussbaum Blask, A.R., *et al.* Color Doppler sonography and scintigraphy of the testis: a prospective, comparative analysis in children with acute scrotal pain. Pediatr Emerg Care, 2002. 18: 67.
https://www.ncbi.nlm.nih.gov/pubmed/11973493
158. Paltiel, H.J., *et al.* Acute scrotal symptoms in boys with an indeterminate clinical presentation: comparison of color Doppler sonography and scintigraphy. Radiology, 1998. 207: 223.
http://pubs.rsna.org/doi/abs/10.1148/radiology.207.1.9530319
159. Terai, A., *et al.* Dynamic contrast-enhanced subtraction magnetic resonance imaging in diagnostics of testicular torsion. Urology, 2006. 67: 1278.
https://www.ncbi.nlm.nih.gov/pubmed/16765192
160. Yuan, Z., *et al.* Clinical study of scrotum scintigraphy in 49 patients with acute scrotal pain: a comparison with ultrasonography. Ann Nucl Med, 2001. 15: 225.
https://www.ncbi.nlm.nih.gov/pubmed/11545192
161. Karmazyn, B., *et al.* Duplex sonographic findings in children with torsion of the testicular appendages: overlap with epididymitis and epididymoorchitis. J Pediatr Surg, 2006. 41: 500.
https://www.ncbi.nlm.nih.gov/pubmed/16516624
162. Lau, P., *et al.* Acute epididymitis in boys: are antibiotics indicated? Br J Urol, 1997. 79: 797.
https://www.ncbi.nlm.nih.gov/pubmed/9158522
163. Abul, F., *et al.* The acute scrotum: a review of 40 cases. Med Princ Pract, 2005. 14: 177.
https://www.ncbi.nlm.nih.gov/pubmed/15863992
164. Cornel, E.B., *et al.* Manual derotation of the twisted spermatic cord. BJU Int, 1999. 83: 672.
https://www.ncbi.nlm.nih.gov/pubmed/10233577
165. Garel, L., *et al.* Preoperative manual detorsion of the spermatic cord with Doppler ultrasound monitoring in patients with intravaginal acute testicular torsion. Pediatr Radiol, 2000. 30: 41.
https://www.ncbi.nlm.nih.gov/pubmed/10663509
166. Sessions, A.E., *et al.* Testicular torsion: direction, degree, duration and disinformation. J Urol, 2003. 169: 663.
https://www.ncbi.nlm.nih.gov/pubmed/12544339
167. Visser, A.J., *et al.* Testicular function after torsion of the spermatic cord. BJU Int, 2003. 92: 200.
https://www.ncbi.nlm.nih.gov/pubmed/12887467
168. Tryfonas, G., *et al.* Late postoperative results in males treated for testicular torsion during childhood. J Pediatr Surg, 1994. 29: 553.
https://www.ncbi.nlm.nih.gov/pubmed/8014814
169. Anderson, M.J., *et al.* Semen quality and endocrine parameters after acute testicular torsion. J Urol, 1992. 147: 1545.
https://www.ncbi.nlm.nih.gov/pubmed/1593686
170. Arap, M.A., *et al.* Late hormonal levels, semen parameters, and presence of antisperm antibodies in patients treated for testicular torsion. J Androl, 2007. 28: 528.
https://www.ncbi.nlm.nih.gov/pubmed/17287456
171. Mor, Y., *et al.* Testicular fixation following torsion of the spermatic cord--does it guarantee prevention of recurrent torsion events? J Urol, 2006. 175: 171.
https://www.ncbi.nlm.nih.gov/pubmed/16406900
172. Figueroa, V., *et al.* Comparative analysis of detorsion alone versus detorsion and tunica albuginea decompression (fasciotomy) with tunica vaginalis flap coverage in the surgical management of prolonged testicular ischemia. J Urol, 2012. 188: 1417.
https://www.ncbi.nlm.nih.gov/pubmed/22906680

173. Akcora, B., *et al.* The protective effect of darbepoetin alfa on experimental testicular torsion and detorsion injury. Int J Urol, 2007. 14: 846.
https://www.ncbi.nlm.nih.gov/pubmed/17760753
174. Aksoy, H., *et al.* Dehydroepiandrosterone treatment attenuates reperfusion injury after testicular torsion and detorsion in rats. J Pediatr Surg, 2007. 42: 1740.
https://www.ncbi.nlm.nih.gov/pubmed/17923206
175. Haj, M., *et al.* Effect of external scrotal cooling on the viability of the testis with torsion in rats. Eur Surg Res, 2007. 39: 160.
https://www.ncbi.nlm.nih.gov/pubmed/17341878
176. Unal, D., *et al.* Protective effects of trimetazidine on testicular ischemia-reperfusion injury in rats. Urol Int, 2007. 78: 356.
https://www.ncbi.nlm.nih.gov/pubmed/17495496
177. Yazihan, N., *et al.* Protective role of erythropoietin during testicular torsion of the rats. World J Urol, 2007. 25: 531.
https://www.ncbi.nlm.nih.gov/pubmed/17690891
178. Lian, B.S., *et al.* Factors Predicting Testicular Atrophy after Testicular Salvage following Torsion. Eur J Pediatr Surg, 2016. 26: 17.
https://www.ncbi.nlm.nih.gov/pubmed/26509312
179. Philip, J., *et al.* Mumps orchitis in the non-immune postpubertal male: a resurgent threat to male fertility? BJU Int, 2006. 97: 138.
https://www.ncbi.nlm.nih.gov/pubmed/16336344
180. Gielchinsky, I., *et al.* Pregnancy Rates after Testicular Torsion. J Urol, 2016. 196: 852.
https://www.ncbi.nlm.nih.gov/pubmed/27117442
181. Bergman, J.E., *et al.* Epidemiology of hypospadias in Europe: a registry-based study. World J Urol, 2015. 33: 2159.
https://www.ncbi.nlm.nih.gov/pubmed/25712311
182. Morera, A.M., *et al.* A study of risk factors for hypospadias in the Rhone-Alpes region (France). J Pediatr Urol, 2006. 2: 169.
https://www.ncbi.nlm.nih.gov/pubmed/18947603
183. van der Zanden, L.F., *et al.* Exploration of gene-environment interactions, maternal effects and parent of origin effects in the etiology of hypospadias. J Urol, 2012. 188: 2354.
https://www.ncbi.nlm.nih.gov/pubmed/23088992
184. Springer, A., *et al.* Worldwide prevalence of hypospadias. J Pediatr Urol, 2016. 12: 152 e1.
https://www.ncbi.nlm.nih.gov/pubmed/26810252
185. Fredell, L., *et al.* Heredity of hypospadias and the significance of low birth weight. J Urol, 2002. 167: 1423.
https://www.ncbi.nlm.nih.gov/pubmed/11832761
186. Lund, L., *et al.* Prevalence of hypospadias in Danish boys: a longitudinal study, 1977-2005. Eur Urol, 2009. 55: 1022.
https://www.ncbi.nlm.nih.gov/pubmed/19155122
187. Mouriquand, O.D., *et al.*, Hypospadias., in Pediatric Urology, 2001, WB Saunders: Philadelphia.
188. van Rooij, I.A., *et al.* Risk factors for different phenotypes of hypospadias: results from a Dutch case-control study. BJU Int, 2013. 112: 121.
https://www.ncbi.nlm.nih.gov/pubmed/23305310
189. Norgaard, M., *et al.* Maternal use of oral contraceptives during early pregnancy and risk of hypospadias in male offspring. Urology, 2009. 74: 583.
https://www.ncbi.nlm.nih.gov/pubmed/19592074
190. Netto, J.M., *et al.* Hormone therapy in hypospadias surgery: a systematic review. J Pediatr Urol, 2013. 9: 971.
https://www.ncbi.nlm.nih.gov/pubmed/23602841
191. Chariatte, V., *et al.* Uroradiological screening for upper and lower urinary tract anomalies in patients with hypospadias: a systematic literature review. Evid Based Med, 2013. 18: 11.
https://www.ncbi.nlm.nih.gov/pubmed/22815315
192. Belman, A.B., Hypospadias and chordee, in Clinical Pediatric Urology 2002, Martin Dunitz: London.
193. Malik, R.D., *et al.* Survey of pediatric urologists on the preoperative use of testosterone in the surgical correction of hypospadias. J Pediatr Urol, 2014.
https://www.ncbi.nlm.nih.gov/pubmed/24726783
194. Wright, I., *et al.* Effect of preoperative hormonal stimulation on postoperative complication rates after proximal hypospadias repair: a systematic review. J Urol, 2013. 190: 652.
https://www.ncbi.nlm.nih.gov/pubmed/23597451

195. Kaya, C., *et al.* The role of pre-operative androgen stimulation in hypospadias surgery. Transl Androl Urol, 2014. 3: 340.
https://www.ncbi.nlm.nih.gov/pubmed/26816790
196. Bush, N.C., *et al.* Age does not impact risk for urethroplasty complications after tubularized incised plate repair of hypospadias in prepubertal boys. J Pediatr Urol, 2013. 9: 252.
https://www.ncbi.nlm.nih.gov/pubmed/22542204
197. Perlmutter, A.E., *et al.* Impact of patient age on distal hypospadias repair: a surgical perspective. Urology, 2006. 68: 648.
https://www.ncbi.nlm.nih.gov/pubmed/16979730
198. Bhat, A., *et al.* Comparison of variables affecting the surgical outcomes of tubularized incised plate urethroplasty in adult and pediatric hypospadias. J Pediatr Urol, 2016. 12: 108 e1.
https://www.ncbi.nlm.nih.gov/pubmed/26778183
199. Castagnetti, M., *et al.* Surgical management of primary severe hypospadias in children: systematic 20-year review. J Urol, 2010. 184: 1469.
https://www.ncbi.nlm.nih.gov/pubmed/20727541
200. Baskin, L.S., *et al.* Changing concepts of hypospadias curvature lead to more onlay island flap procedures. J Urol, 1994. 151: 191.
https://www.ncbi.nlm.nih.gov/pubmed/8254812
201. Hollowell, J.G., *et al.* Preservation of the urethral plate in hypospadias repair: extended applications and further experience with the onlay island flap urethroplasty. J Urol, 1990. 143: 98.
https://www.ncbi.nlm.nih.gov/pubmed/2294275
202. Snodgrass, W., *et al.* Straightening ventral curvature while preserving the urethral plate in proximal hypospadias repair. J Urol, 2009. 182: 1720.
https://www.ncbi.nlm.nih.gov/pubmed/19692004
203. Braga, L.H., *et al.* Ventral penile lengthening versus dorsal plication for severe ventral curvature in children with proximal hypospadias. J Urol, 2008. 180: 1743.
https://www.ncbi.nlm.nih.gov/pubmed/18721961
204. el-Kassaby, A.W., *et al.* Modified tubularized incised plate urethroplasty for hypospadias repair: a long-term results of 764 patients. Urology, 2008. 71: 611.
https://www.ncbi.nlm.nih.gov/pubmed/18295308
205. El-Sherbiny, M.T., *et al.* Comprehensive analysis of tubularized incised-plate urethroplasty in primary and re-operative hypospadias. BJU Int, 2004. 93: 1057.
https://www.ncbi.nlm.nih.gov/pubmed/15142164
206. Orkiszewski, M., *et al.* Morphology and urodynamics after longitudinal urethral plate incision in proximal hypospadias repairs: long-term results. Eur J Pediatr Surg, 2004. 14: 35.
https://www.ncbi.nlm.nih.gov/pubmed/15024677
207. Snodgrass, W.T., *et al.* Tubularized incised plate hypospadias repair for distal hypospadias. J Pediatr Urol, 2010. 6: 408.
https://www.ncbi.nlm.nih.gov/pubmed/17222659
208. Pfistermuller, K.L., *et al.* Meta-analysis of complication rates of the tubularized incised plate (TIP) repair. J Pediatr Urol, 2015. 11: 54.
https://www.ncbi.nlm.nih.gov/pubmed/25819601
209. Schwentner, C., *et al.* Interim outcome of the single stage dorsal inlay skin graft for complex hypospadias reoperations. J Urol, 2006. 175: 1872.
https://www.ncbi.nlm.nih.gov/pubmed/16600785
210. Ahmed, M., *et al.* Is combined inner preputial inlay graft with tubularized incised plate in hypospadias repair worth doing? J Pediatr Urol, 2015. 11: 229 e1.
https://www.ncbi.nlm.nih.gov/pubmed/26119452
211. Pippi Salle, J.L., *et al.* Proximal hypospadias: A persistent challenge. Single institution outcome analysis of three surgical techniques over a 10-year period. J Pediatr Urol, 2016. 12: 28 e1.
https://www.ncbi.nlm.nih.gov/pubmed/26279102
212. Meyer-Junghanel, L., *et al.* Experience with repair of 120 hypospadias using Mathieu's procedure. Eur J Pediatr Surg, 1995. 5: 355.
https://www.ncbi.nlm.nih.gov/pubmed/8773227
213. Snodgrass, W.T., *et al.* Urethral strictures following urethral plate and proximal urethral elevation during proximal TIP hypospadias repair. J Pediatr Urol, 2013. 9: 990.
https://www.ncbi.nlm.nih.gov/pubmed/23707201
214. Cambareri, G.M., *et al.* Hypospadias repair with onlay preputial graft: a 25-year experience with long-term follow-up. BJU Int, 2016. 118: 451.
https://www.ncbi.nlm.nih.gov/pubmed/26780179

215. Perovic, S., *et al.* Onlay island flap urethroplasty for severe hypospadias: a variant of the technique. J Urol, 1994. 151: 711.
https://www.ncbi.nlm.nih.gov/pubmed/8308994
216. Kocvara, R., *et al.* Inlay-onlay flap urethroplasty for hypospadias and urethral stricture repair. J Urol, 1997. 158: 2142.
https://www.ncbi.nlm.nih.gov/pubmed/9366331
217. Castagnetti, M., *et al.* Primary severe hypospadias: comparison of reoperation rates and parental perception of urinary symptoms and cosmetic outcomes among 4 repairs. J Urol, 2013. 189: 1508.
https://www.ncbi.nlm.nih.gov/pubmed/23154207
218. Koyanagi, T., *et al.* One-stage repair of hypospadias: is there no simple method universally applicable to all types of hypospadias? J Urol, 1994. 152: 1232.
https://www.ncbi.nlm.nih.gov/pubmed/8072111
219. Hayashi, Y., *et al.* Neo-modified Koyanagi technique for the single-stage repair of proximal hypospadias. J Pediatr Urol, 2007. 3: 239.
https://www.ncbi.nlm.nih.gov/pubmed/18947743
220. Catti, M., *et al.* Original Koyanagi urethroplasty versus modified Hayashi technique: outcome in 57 patients. J Pediatr Urol, 2009. 5: 300.
https://www.ncbi.nlm.nih.gov/pubmed/19457720
221. DeFoor, W., *et al.* Results of single staged hypospadias surgery to repair penoscrotal hypospadias with bifid scrotum or penoscrotal transposition. J Urol, 2003. 170: 1585.
https://www.ncbi.nlm.nih.gov/pubmed/14501667
222. Bracka, A. Hypospadias repair: the two-stage alternative. Br J Urol, 1995. 76 Suppl 3: 31.
https://www.ncbi.nlm.nih.gov/pubmed/8535768
223. Lam, P.N., *et al.* 2-stage repair in infancy for severe hypospadias with chordee: long-term results after puberty. J Urol, 2005. 174: 1567.
https://www.ncbi.nlm.nih.gov/pubmed/16148653
224. Stanasel, I., *et al.* Complications following Staged Hypospadias Repair Using Transposed Preputial Skin Flaps. J Urol, 2015. 194: 512.
https://www.ncbi.nlm.nih.gov/pubmed/25701546
225. Ahmed, S., *et al.* Buccal mucosal graft for secondary hypospadias repair and urethral replacement. Br J Urol, 1997. 80: 328.
https://www.ncbi.nlm.nih.gov/pubmed/9284210
226. Mokhless, I.A., *et al.* The multistage use of buccal mucosa grafts for complex hypospadias: histological changes. J Urol, 2007. 177: 1496.
https://www.ncbi.nlm.nih.gov/pubmed/17382762
227. Castagnetti, M., *et al.* Does Preputial Reconstruction Increase Complication Rate of Hypospadias Repair? 20-Year Systematic Review and Meta-Analysis. Front Pediatr, 2016. 4: 41.
https://www.ncbi.nlm.nih.gov/pubmed/27200322
228. Hsieh, M.H., *et al.* Surgical antibiotic practices among pediatric urologists in the United States. J Pediatr Urol, 2011. 7: 192.
https://www.ncbi.nlm.nih.gov/pubmed/20537590
229. Chalmers, D.J., *et al.* Distal hypospadias repair in infants without a postoperative stent. Pediatr Surg Int, 2015. 31: 287.
https://www.ncbi.nlm.nih.gov/pubmed/25475503
230. Meir, D.B., *et al.* Is prophylactic antimicrobial treatment necessary after hypospadias repair? J Urol, 2004. 171: 2621.
https://www.ncbi.nlm.nih.gov/pubmed/15118434
231. Kanaroglou, N., *et al.* Is there a role for prophylactic antibiotics after stented hypospadias repair? J Urol, 2013. 190: 1535.
https://www.ncbi.nlm.nih.gov/pubmed/23416639
232. Bush, N.C., *et al.* Glans size is an independent risk factor for urethroplasty complications after hypospadias repair. J Pediatr Urol, 2015. 11: 355 e1.
https://www.ncbi.nlm.nih.gov/pubmed/26320396
233. Lee, O.T., *et al.* Predictors of secondary surgery after hypospadias repair: a population based analysis of 5,000 patients. J Urol, 2013. 190: 251.
https://www.ncbi.nlm.nih.gov/pubmed/23376710
234. Braga, L.H., *et al.* Tubularized incised plate urethroplasty for distal hypospadias: A literature review. Indian J Urol, 2008. 24: 219.
https://www.ncbi.nlm.nih.gov/pubmed/19468401

235. Wilkinson, D.J., *et al.* Outcomes in distal hypospadias: a systematic review of the Mathieu and tubularized incised plate repairs. J Pediatr Urol, 2012. 8: 307.
https://www.ncbi.nlm.nih.gov/pubmed/21159560
236. Wang, F., *et al.* Systematic review and meta-analysis of studies comparing the perimeatal-based flap and tubularized incised-plate techniques for primary hypospadias repair. Pediatr Surg Int, 2013. 29: 811.
https://www.ncbi.nlm.nih.gov/pubmed/23793987
237. Leslie, B., *et al.* Critical outcome analysis of staged buccal mucosa graft urethroplasty for prior failed hypospadias repair in children. J Urol, 2011. 185: 1077.
https://www.ncbi.nlm.nih.gov/pubmed/21256520
238. Spinoit, A.F., *et al.* Hypospadias repair at a tertiary care center: long-term followup is mandatory to determine the real complication rate. J Urol, 2013. 189: 2276.
https://www.ncbi.nlm.nih.gov/pubmed/23306089
239. Andersson, M., *et al.* Hypospadias repair with tubularized incised plate: Does the obstructive flow pattern resolve spontaneously? J Pediatr Urol, 2011. 7: 441.
https://www.ncbi.nlm.nih.gov/pubmed/20630805
240. Gonzalez, R., *et al.* Importance of urinary flow studies after hypospadias repair: a systematic review. Int J Urol, 2011. 18: 757.
https://www.ncbi.nlm.nih.gov/pubmed/21883491
241. Andersson, M., *et al.* Normalized Urinary Flow at Puberty after Tubularized Incised Plate Urethroplasty for Hypospadias in Childhood. J Urol, 2015. 194: 1407.
https://www.ncbi.nlm.nih.gov/pubmed/26087380
242. Hueber, P.A., *et al.* Long-term functional outcomes of distal hypospadias repair: a single center retrospective comparative study of TIPs, Mathieu and MAGPI. J Pediatr Urol, 2015. 11: 68 e1.
https://www.ncbi.nlm.nih.gov/pubmed/25824882
243. Perera, M., *et al.* Long-term urethral function measured by uroflowmetry after hypospadias surgery: comparison with an age matched control. J Urol, 2012. 188: 1457.
https://www.ncbi.nlm.nih.gov/pubmed/22906660
244. Holland, A.J., *et al.* HOSE: an objective scoring system for evaluating the results of hypospadias surgery. BJU Int, 2001. 88: 255.
https://www.ncbi.nlm.nih.gov/pubmed/11488741
245. van der Toorn, F., *et al.* Introducing the HOPE (Hypospadias Objective Penile Evaluation)-score: a validation study of an objective scoring system for evaluating cosmetic appearance in hypospadias patients. J Pediatr Urol, 2013. 9: 1006.
https://www.ncbi.nlm.nih.gov/pubmed/23491983
246. Weber, D.M., *et al.* The Penile Perception Score: an instrument enabling evaluation by surgeons and patient self-assessment after hypospadias repair. J Urol, 2013. 189: 189.
https://www.ncbi.nlm.nih.gov/pubmed/23174225
247. Moriya, K., *et al.* Long-term cosmetic and sexual outcome of hypospadias surgery: norm related study in adolescence. J Urol, 2006. 176: 1889.
https://www.ncbi.nlm.nih.gov/pubmed/16945681
248. Rynja, S.P., *et al.* Functional, cosmetic and psychosexual results in adult men who underwent hypospadias correction in childhood. J Pediatr Urol, 2011. 7: 504.
https://www.ncbi.nlm.nih.gov/pubmed/21429804
249. Ortqvist, L., *et al.* Long-term followup of men born with hypospadias: urological and cosmetic results. J Urol, 2015. 193: 975.
https://www.ncbi.nlm.nih.gov/pubmed/25268894
250. Adams, J., *et al.* Reconstructive surgery for hypospadias: A systematic review of long-term patient satisfaction with cosmetic outcomes. Indian J Urol, 2016. 32: 93.
https://www.ncbi.nlm.nih.gov/pubmed/27127350
251. Nyirady, P., *et al.* Management of congenital penile curvature. J Urol, 2008. 179: 1495.
https://www.ncbi.nlm.nih.gov/pubmed/18295273
252. Baskin, L.S., *et al.* Neuroanatomical ontogeny of the human fetal penis. Br J Urol, 1997. 79: 628.
https://www.ncbi.nlm.nih.gov/pubmed/9126098
253. Ebbehoj, J., *et al.* Congenital penile angulation. Br J Urol, 1987. 60: 264.
https://www.ncbi.nlm.nih.gov/pubmed/3676675
254. Kelami, A. Congenital penile deviation and its treatment with the Nesbit-Kelami technique. Br J Urol, 1987. 60: 261.
https://www.ncbi.nlm.nih.gov/pubmed/3676674

255. Yachia, D., *et al.* The incidence of congenital penile curvature. J Urol, 1993. 150: 1478. https://www.ncbi.nlm.nih.gov/pubmed/8411431
256. Hsieh, J.T., *et al.* Correction of congenital penile curvature using modified tunical plication with absorbable sutures: the long-term outcome and patient satisfaction. Eur Urol, 2007. 52: 261. https://www.ncbi.nlm.nih.gov/pubmed/17234333
257. Sasso, F., *et al.* Penile curvature: an update for management from 20 years experience in a high volume centre. Urologia, 2016. 83: 130. https://www.ncbi.nlm.nih.gov/pubmed/27103093
258. Gittes, R.F., *et al.* Injection technique to induce penile erection. Urology, 1974. 4: 473. https://www.ncbi.nlm.nih.gov/pubmed/4418594
259. Schultheiss, D., *et al.* Congenital and acquired penile deviation treated with the essed plication method. Eur Urol, 2000. 38: 167. https://www.ncbi.nlm.nih.gov/pubmed/10895008
260. Yachia, D. Modified corporoplasty for the treatment of penile curvature. J Urol, 1990. 143: 80. https://www.ncbi.nlm.nih.gov/pubmed/2294269
261. Rehman, J., *et al.* Results of surgical treatment for abnormal penile curvature: Peyronie's disease and congenital deviation by modified Nesbit plication (tunical shaving and plication). J Urol, 1997. 157: 1288. https://www.ncbi.nlm.nih.gov/pubmed/9120923
262. Poulsen, J., *et al.* Treatment of penile curvature--a retrospective study of 175 patients operated with plication of the tunica albuginea or with the Nesbit procedure. Br J Urol, 1995. 75: 370. https://www.ncbi.nlm.nih.gov/pubmed/7735803
263. Leonardo, C., *et al.* Plication corporoplasty versus Nesbit operation for the correction of congenital penile curvature. A long-term follow-up. Int Urol Nephrol, 2012. 44: 55. https://www.ncbi.nlm.nih.gov/pubmed/21559790
264. Cavallini, G., *et al.* Pilot study to determine improvements in subjective penile morphology and personal relationships following a Nesbit plication procedure for men with congenital penile curvature. Asian J Androl, 2008. 10: 512. https://www.ncbi.nlm.nih.gov/pubmed/18097530
265. Vatne, V., *et al.* Functional results after operations of penile deviations: an institutional experience. Scand J Urol Nephrol Suppl, 1996. 179: 151. https://www.ncbi.nlm.nih.gov/pubmed/8908683
266. Shaeer, O., *et al.* Shaeer's Corporal Rotation III: Shortening-Free Correction of Congenital Penile Curvature-The Noncorporotomy Technique. Eur Urol, 2016. 69: 129. https://www.ncbi.nlm.nih.gov/pubmed/26298209
267. Akbay, E., *et al.* The prevalence of varicocele and varicocele-related testicular atrophy in Turkish children and adolescents. BJU Int, 2000. 86: 490. https://www.ncbi.nlm.nih.gov/pubmed/10971279
268. Kogan, S.J., The pediatric varicocele. In: Pediatric urology, 2001, WB Saunders: Philadelphia.
269. Oster, J. Varicocele in children and adolescents. An investigation of the incidence among Danish school children. Scand J Urol Nephrol, 1971. 5: 27. https://www.ncbi.nlm.nih.gov/pubmed/5093090
270. Kass, E.J., *et al.* Reversal of testicular growth failure by varicocele ligation. J Urol, 1987. 137: 475. https://www.ncbi.nlm.nih.gov/pubmed/3820376
271. Paduch, D.A., *et al.* Repair versus observation in adolescent varicocele: a prospective study. J Urol, 1997. 158: 1128. https://www.ncbi.nlm.nih.gov/pubmed/9258155
272. Li, F., *et al.* Effect of varicocelectomy on testicular volume in children and adolescents: a meta-analysis. Urology, 2012. 79: 1340. https://www.ncbi.nlm.nih.gov/pubmed/22516359
273. Kocvara, R., *et al.* Division of lymphatic rvessels at varicocelectomy leads to testicular oedema and decline in testicular function according to the LH-RH analogue stimulation test. Eur Urol, 2003. 43: 430. https://www.ncbi.nlm.nih.gov/pubmed/12667726
274. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. World Health Organization. Fertil Steril, 1992. 57: 1289. https://www.ncbi.nlm.nih.gov/pubmed/1601152
275. Laven, J.S., *et al.* Effects of varicocele treatment in adolescents: a randomized study. Fertil Steril, 1992. 58: 756. https://www.ncbi.nlm.nih.gov/pubmed/1426322

276. Okuyama, A., *et al.* Surgical repair of varicocele at puberty: preventive treatment for fertility improvement. J Urol, 1988. 139: 562.
https://www.ncbi.nlm.nih.gov/pubmed/3343743
277. Pinto, K.J., *et al.* Varicocele related testicular atrophy and its predictive effect upon fertility. J Urol, 1994. 152: 788.
https://www.ncbi.nlm.nih.gov/pubmed/8022015
278. Nork, J.J., *et al.* Youth varicocele and varicocele treatment: a meta-analysis of semen outcomes. Fertil Steril, 2014. 102: 381.
https://www.ncbi.nlm.nih.gov/pubmed/24907913
279. Dubin, L., *et al.* Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. Fertil Steril, 1970. 21: 606.
https://www.ncbi.nlm.nih.gov/pubmed/5433164
280. Tasci, A.I., *et al.* Color doppler ultrasonography and spectral analysis of venous flow in diagnosis of varicocele. Eur Urol, 2001. 39: 316.
https://www.ncbi.nlm.nih.gov/pubmed/11275726
281. Diamond, D.A., *et al.* Relationship of varicocele grade and testicular hypotrophy to semen parameters in adolescents. J Urol, 2007. 178: 1584.
https://www.ncbi.nlm.nih.gov/pubmed/17707046
282. Aragona, F., *et al.* Correlation of testicular volume, histology and LHRH test in adolescents with idiopathic varicocele. Eur Urol, 1994. 26: 61.
https://www.ncbi.nlm.nih.gov/pubmed/7925532
283. Bogaert, G., *et al.* Pubertal screening and treatment for varicocele do not improve chance of paternity as adult. J Urol, 2013. 189: 2298.
https://www.ncbi.nlm.nih.gov/pubmed/23261480
284. Chen, J.J., *et al.* Is the comparison of a left varicocele testis to its contralateral normal testis sufficient in determining its well-being? Urology, 2011. 78: 1167.
https://www.ncbi.nlm.nih.gov/pubmed/21782220
285. Goldstein, M., *et al.* Microsurgical inguinal varicocelectomy with delivery of the testis: an artery and lymphatic sparing technique. J Urol, 1992. 148: 1808.
https://www.ncbi.nlm.nih.gov/pubmed/1433614
286. Hopps, C.V., *et al.* Intraoperative varicocele anatomy: a microscopic study of the inguinal versus subinguinal approach. J Urol, 2003. 170: 2366.
https://www.ncbi.nlm.nih.gov/pubmed/14634418
287. Kocvara, R., *et al.* Lymphatic sparing laparoscopic varicocelectomy: a microsurgical repair. J Urol, 2005. 173: 1751.
https://www.ncbi.nlm.nih.gov/pubmed/15821575
288. Riccabona, M., *et al.* Optimizing the operative treatment of boys with varicocele: sequential comparison of 4 techniques. J Urol, 2003. 169: 666.
https://www.ncbi.nlm.nih.gov/pubmed/12544340
289. Marmar, J., *et al.* New scientific information related to varicoceles. J Urol, 2003. 170: 2371.
https://www.ncbi.nlm.nih.gov/pubmed/14634419
290. Minevich, E., *et al.* Inguinal microsurgical varicocelectomy in the adolescent: technique and preliminary results. J Urol, 1998. 159: 1022.
https://www.ncbi.nlm.nih.gov/pubmed/9474223
291. Mirilas, P., *et al.* Microsurgical subinguinal varicocelectomy in children, adolescents, and adults: surgical anatomy and anatomically justified technique. J Androl, 2012. 33: 338.
https://www.ncbi.nlm.nih.gov/pubmed/21835913
292. Oswald, J., *et al.* The use of isosulphan blue to identify lymphatic vessels in high retroperitoneal ligation of adolescent varicocele--avoiding postoperative hydrocele. BJU Int, 2001. 87: 502.
https://www.ncbi.nlm.nih.gov/pubmed/11298043
293. Esposito, C., *et al.* Technical standardization of laparoscopic lymphatic sparing varicocelectomy in children using isosulfan blue. J Pediatr Surg, 2014. 49: 660.
https://www.ncbi.nlm.nih.gov/pubmed/24726132
294. Kim, K.S., *et al.* Impact of internal spermatic artery preservation during laparoscopic varicocelectomy on recurrence and the catch-up growth rate in adolescents. J Pediatr Urol, 2014. 10: 435.
https://www.ncbi.nlm.nih.gov/pubmed/24314819
295. Fast, A.M., *et al.* Adolescent varicocelectomy: does artery sparing influence recurrence rate and/or catch-up growth? Andrology, 2014. 2: 159.
https://www.ncbi.nlm.nih.gov/pubmed/24339439

296. Fayad, F., *et al.* Percutaneous retrograde endovascular occlusion for pediatric varicocele. J Pediatr Surg, 2011. 46: 525.
https://www.ncbi.nlm.nih.gov/pubmed/21376204
297. Thon, W.F., *et al.* Percutaneous sclerotherapy of idiopathic varicocele in childhood: a preliminary report. J Urol, 1989. 141: 913.
https://www.ncbi.nlm.nih.gov/pubmed/2926889
298. Hoberman, A., *et al.* Prevalence of urinary tract infection in febrile infants. J Pediatr, 1993. 123: 17.
https://www.ncbi.nlm.nih.gov/pubmed/8320616
299. Marild, S., *et al.* Incidence rate of first-time symptomatic urinary tract infection in children under 6 years of age. Acta Paediatr, 1998. 87: 549.
https://www.ncbi.nlm.nih.gov/pubmed/9641738
300. O'Brien, K., *et al.* Prevalence of urinary tract infection (UTI) in sequential acutely unwell children presenting in primary care: exploratory study. Scand J Prim Health Care, 2011. 29: 19.
https://www.ncbi.nlm.nih.gov/pubmed/21323495
301. Kunin, C.M., *et al.* Sensitivity of a nitrite indicator strip method in detecting bacteriuria in preschool girls. Pediatrics, 1977. 60: 244.
https://www.ncbi.nlm.nih.gov/pubmed/887340
302. Shaikh, N., *et al.* Prevalence of urinary tract infection in childhood: a meta-analysis. Pediatr Infect Dis J, 2008. 27: 302.
https://www.ncbi.nlm.nih.gov/pubmed/18316994
303. Winberg, J., *et al.* Epidemiology of symptomatic urinary tract infection in childhood. Acta Paediatr Scand Suppl, 1974: 1.
https://www.ncbi.nlm.nih.gov/pubmed/4618418
304. Zorc, J.J., *et al.* Clinical and demographic factors associated with urinary tract infection in young febrile infants. Pediatrics, 2005. 116: 644.
https://www.ncbi.nlm.nih.gov/pubmed/16140703
305. Rushton, H.G., *et al.* Pyelonephritis in male infants: how important is the foreskin? J Urol, 1992. 148: 733.
https://www.ncbi.nlm.nih.gov/pubmed/1640557
306. Magin, E.C., *et al.* Efficacy of short-term intravenous antibiotic in neonates with urinary tract infection. Pediatr Emerg Care, 2007. 23: 83.
https://www.ncbi.nlm.nih.gov/pubmed/17351406
307. Sastre, J.B., *et al.* Urinary tract infection in the newborn: clinical and radio imaging studies. Pediatr Nephrol, 2007. 22: 1735.
https://www.ncbi.nlm.nih.gov/pubmed/17665222
308. Shortliffe, L.M.D., *et al.*, Pediatric urinary tract infections. in Pediatric Urology, 2001, Saunders: Philadelphia.
309. Burns, M.W., *et al.* Pediatric urinary tract infection. Diagnosis, classification, and significance. Pediatr Clin North Am, 1987. 34: 1111.
https://www.ncbi.nlm.nih.gov/pubmed/3658502
310. Beetz, R., *et al.* [Urinary tract infections in infants and children -- a consensus on diagnostic, therapy and prophylaxis]. Urologe A, 2007. 46: 112.
https://www.ncbi.nlm.nih.gov/pubmed/17225140
311. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. Pediatrics, 1999. 103: 843.
https://www.ncbi.nlm.nih.gov/pubmed/10103321
312. Craig, J.C., *et al.* The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: prospective cohort study of 15 781 febrile illnesses. Bmj, 2010. 340: c1594.
https://www.ncbi.nlm.nih.gov/pubmed/20406860
313. Lin, D.S., *et al.* Urinary tract infection in febrile infants younger than eight weeks of Age. Pediatrics, 2000. 105: E20.
https://www.ncbi.nlm.nih.gov/pubmed/10654980
314. Tullus, K. Difficulties in diagnosing urinary tract infections in small children. Pediatr Nephrol, 2011. 26: 1923.
https://www.ncbi.nlm.nih.gov/pubmed/21773821
315. Whiting, P., *et al.* Rapid tests and urine sampling techniques for the diagnosis of urinary tract infection (UTI) in children under five years: a systematic review. BMC Pediatr, 2005. 5: 4.
https://www.ncbi.nlm.nih.gov/pubmed/15811182

316. Koch, V.H., *et al.* [Urinary tract infection: a search for evidence]. J Pediatr (Rio J), 2003. 79 Suppl 1: S97.
https://www.ncbi.nlm.nih.gov/pubmed/14506522
317. Ma, J.F., *et al.* Urinary tract infection in children: etiology and epidemiology. Urol Clin North Am, 2004. 31: 517.
https://www.ncbi.nlm.nih.gov/pubmed/15313061
318. Ramage, I.J., *et al.* Accuracy of clean-catch urine collection in infancy. J Pediatr, 1999. 135: 765.
https://www.ncbi.nlm.nih.gov/pubmed/10586183
319. Roberts, K.B., *et al.* Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics, 2011. 128: 595.
https://www.ncbi.nlm.nih.gov/pubmed/21873693
320. Tosif, S., *et al.* Contamination rates of different urine collection methods for the diagnosis of urinary tract infections in young children: an observational cohort study. J Paediatr Child Health, 2012. 48: 659.
https://www.ncbi.nlm.nih.gov/pubmed/22537082
321. Austin, B.J., *et al.* Is urethral catheterization a successful alternative to suprapubic aspiration in neonates? J Paediatr Child Health, 1999. 35: 34.
https://www.ncbi.nlm.nih.gov/pubmed/10234632
322. Wingerter, S., *et al.* Risk factors for contamination of catheterized urine specimens in febrile children. Pediatr Emerg Care, 2011. 27: 1.
https://www.ncbi.nlm.nih.gov/pubmed/21178815
323. Buys, H., *et al.* Suprapubic aspiration under ultrasound guidance in children with fever of undiagnosed cause. Bmj, 1994. 308: 690.
https://www.ncbi.nlm.nih.gov/pubmed/8142792
324. Kiernan, S.C., *et al.* Ultrasound guidance of suprapubic bladder aspiration in neonates. J Pediatr, 1993. 123: 789.
https://www.ncbi.nlm.nih.gov/pubmed/8142792
325. Hildebrand, W.L., *et al.* Suprapubic bladder aspiration in infants. Am Fam Physician, 1981. 23: 115.
https://www.ncbi.nlm.nih.gov/pubmed/7234629
326. Kozer, E., *et al.* Pain in infants who are younger than 2 months during suprapubic aspiration and transurethral bladder catheterization: a randomized, controlled study. Pediatrics, 2006. 118: e51.
https://www.ncbi.nlm.nih.gov/pubmed/16818537
327. Vaillancourt, S., *et al.* To clean or not to clean: effect on contamination rates in midstream urine collections in toilet-trained children. Pediatrics, 2007. 119: e1288.
https://www.ncbi.nlm.nih.gov/pubmed/17502345
328. Powell, H.R., *et al.* Urinary nitrite in symptomatic and asymptomatic urinary infection. Arch Dis Child, 1987. 62: 138.
https://www.ncbi.nlm.nih.gov/pubmed/3548604
329. Stull, T.L., *et al.* Epidemiology and natural history of urinary tract infections in children. Med Clin North Am, 1991. 75: 287.
https://www.ncbi.nlm.nih.gov/pubmed/1996034
330. Hoberman, A., *et al.* Is urine culture necessary to rule out urinary tract infection in young febrile children? Pediatr Infect Dis J, 1996. 15: 304.
https://www.ncbi.nlm.nih.gov/pubmed/8866798
331. Herr, S.M., *et al.* Enhanced urinalysis improves identification of febrile infants ages 60 days and younger at low risk for serious bacterial illness. Pediatrics, 2001. 108: 866.
https://www.ncbi.nlm.nih.gov/pubmed/11581437
332. Mayo, S., *et al.* Clinical laboratory automated urinalysis: comparison among automated microscopy, flow cytometry, two test strips analyzers, and manual microscopic examination of the urine sediments. J Clin Lab Anal, 2008. 22: 262.
https://www.ncbi.nlm.nih.gov/pubmed/18623125
333. Kass, E.H. Asymptomatic infections of the urinary tract. Trans Assoc Am Physicians, 1956. 69: 56.
https://www.ncbi.nlm.nih.gov/pubmed/13380946
334. Lohr, J.A. Use of routine urinalysis in making a presumptive diagnosis of urinary tract infection in children. Pediatr Infect Dis J, 1991. 10: 646.
https://www.ncbi.nlm.nih.gov/pubmed/1923675
335. Bollgren, I., *et al.* Low urinary counts of P-fimbriated Escherichia coli in presumed acute pyelonephritis. Arch Dis Child, 1984. 59: 102.
https://www.ncbi.nlm.nih.gov/pubmed/6142697

336. Stamm, W.E. Measurement of pyuria and its relation to bacteriuria. Am J Med, 1983. 75: 53. https://www.ncbi.nlm.nih.gov/pubmed/6349345
337. Grabe, M., *et al.*, EAU Guidelines on Urological Infections. Presented at the EAU Annual Congress, ed. European Association of Urology. 2011, Arnhem, The Netherlands
338. Preda, I., *et al.* Value of ultrasound in evaluation of infants with first urinary tract infection. J Urol, 2010. 183: 1984. https://www.ncbi.nlm.nih.gov/pubmed/20303537
339. Chang, S.J., *et al.* Elevated postvoid residual urine volume predicting recurrence of urinary tract infections in toilet-trained children. Pediatr Nephrol, 2015. 30: 1131. https://www.ncbi.nlm.nih.gov/pubmed/25673516
340. Shiraishi, K., *et al.* Risk factors for breakthrough infection in children with primary vesicoureteral reflux. J Urol, 2010. 183: 1527. https://www.ncbi.nlm.nih.gov/pubmed/20172558
341. Quirino, I.G., *et al.* Combined use of late phase dimercapto-succinic acid renal scintigraphy and ultrasound as first line screening after urinary tract infection in children. J Urol, 2011. 185: 258. https://www.ncbi.nlm.nih.gov/pubmed/21074813
342. Siomou, E., *et al.* Implications of 99mTc-DMSA scintigraphy performed during urinary tract infection in neonates. Pediatrics, 2009. 124: 881. https://www.ncbi.nlm.nih.gov/pubmed/19661052
343. Doganis, D., *et al.* Timing of voiding cystourethrography in infants with first time urinary infection. Pediatr Nephrol, 2009. 24: 319. https://www.ncbi.nlm.nih.gov/pubmed/18853200
344. Sathapornwajana, P., *et al.* Timing of voiding cystourethrogram after urinary tract infection. Arch Dis Child, 2008. 93: 229. https://www.ncbi.nlm.nih.gov/pubmed/17626141
345. Spencer, J.D., *et al.* The accuracy and health risks of a voiding cystourethrogram after a febrile urinary tract infection. J Pediatr Urol, 2012. 8: 72. https://www.ncbi.nlm.nih.gov/pubmed/21126919
346. Hoebeke, P., *et al.* Assessment of lower urinary tract dysfunction in children with non-neuropathic bladder sphincter dysfunction. Eur Urol, 1999. 35: 57. https://www.ncbi.nlm.nih.gov/pubmed/9933796
347. Koff, S.A., *et al.* The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. J Urol, 1998. 160: 1019. https://www.ncbi.nlm.nih.gov/pubmed/9719268
348. van Gool, J.D. Dysfunctional voiding: a complex of bladder/sphincter dysfunction, urinary tract infections and vesicoureteral reflux. Acta Urol Belg, 1995. 63: 27. https://www.ncbi.nlm.nih.gov/pubmed/7484519
349. van Gool, J.D., *et al.* Bladder-sphincter dysfunction, urinary infection and vesico-ureteral reflux with special reference to cognitive bladder training. Contrib Nephrol, 1984. 39: 190. https://www.ncbi.nlm.nih.gov/pubmed/6744871
350. De Paepe, H., *et al.* Pelvic-floor therapy and toilet training in young children with dysfunctional voiding and obstipation. BJU Int, 2000. 85: 889. https://www.ncbi.nlm.nih.gov/pubmed/10792172
351. Loening-Baucke, V. Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. Pediatrics, 1997. 100: 228. https://www.ncbi.nlm.nih.gov/pubmed/9240804
352. O'Regan, S., *et al.* Constipation, bladder instability, urinary tract infection syndrome. Clin Nephrol, 1985. 23: 152. https://www.ncbi.nlm.nih.gov/pubmed/3987104
353. Tutunculer, F., *et al.* Transient Pseudohypoaldosteronism in an infant with urinary tract anomaly. Pediatr Int, 2004. 46: 618. https://www.ncbi.nlm.nih.gov/pubmed/15491397
354. Nandagopal, R., *et al.* Transient Pseudohypoaldosteronism due to Urinary Tract Infection in Infancy: A Report of 4 Cases. Int J Pediatr Endocrinol, 2009. 2009: 195728. https://www.ncbi.nlm.nih.gov/pubmed/19946403
355. Contopoulos-Ioannidis, D.G., *et al.* Extended-interval aminoglycoside administration for children: a meta-analysis. Pediatrics, 2004. 114: e111. https://www.ncbi.nlm.nih.gov/pubmed/15231982

356. Hodson, E.M., *et al.* Antibiotics for acute pyelonephritis in children. Cochrane Database Syst Rev, 2007: CD003772.
https://www.ncbi.nlm.nih.gov/pubmed/17943796
357. Dore-Bergeron, M.J., *et al.* Urinary tract infections in 1- to 3-month-old infants: ambulatory treatment with intravenous antibiotics. Pediatrics, 2009. 124: 16.
https://www.ncbi.nlm.nih.gov/pubmed/19564278
358. Gauthier, M., *et al.* Treatment of urinary tract infections among febrile young children with daily intravenous antibiotic therapy at a day treatment center. Pediatrics, 2004. 114: e469.
https://www.ncbi.nlm.nih.gov/pubmed/15466073
359. Bouissou, F., *et al.* Prospective, randomized trial comparing short and long intravenous antibiotic treatment of acute pyelonephritis in children: dimercaptosuccinic acid scintigraphic evaluation at 9 months. Pediatrics, 2008. 121: e553.
https://www.ncbi.nlm.nih.gov/pubmed/18267977
360. Craig, J.C., *et al.* Antibiotic prophylaxis and recurrent urinary tract infection in children. N Engl J Med, 2009. 361: 1748.
https://www.ncbi.nlm.nih.gov/pubmed/19864673
361. Hoberman, A., *et al.* Oral versus initial intravenous therapy for urinary tract infections in young febrile children. Pediatrics, 1999. 104: 79.
https://www.ncbi.nlm.nih.gov/pubmed/10390264
362. Neuhaus, T.J., *et al.* Randomised trial of oral versus sequential intravenous/oral cephalosporins in children with pyelonephritis. Eur J Pediatr, 2008. 167: 1037.
https://www.ncbi.nlm.nih.gov/pubmed/18074149
363. Montini, G., *et al.* Antibiotic treatment for pyelonephritis in children: multicentre randomised controlled non-inferiority trial. Bmj, 2007. 335: 386.
https://www.ncbi.nlm.nih.gov/pubmed/17611232
364. Mak, R.H., *et al.* Are oral antibiotics alone efficacious for the treatment of a first episode of acute pyelonephritis in children? Nat Clin Pract Nephrol, 2008. 4: 10.
https://www.ncbi.nlm.nih.gov/pubmed/17971799
365. Klar, A., *et al.* Focal bacterial nephritis (lobar nephronia) in children. J Pediatr, 1996. 128: 850.
https://www.ncbi.nlm.nih.gov/pubmed/8648547
366. Cheng, C.H., *et al.* Effective duration of antimicrobial therapy for the treatment of acute lobar nephronia. Pediatrics, 2006. 117: e84.
https://www.ncbi.nlm.nih.gov/pubmed/16326693
367. Ramos, N.L., *et al.* Characterisation of uropathogenic Escherichia coli from children with urinary tract infection in different countries. Eur J Clin Microbiol Infect Dis, 2011. 30: 1587.
https://www.ncbi.nlm.nih.gov/pubmed/21509475
368. Kizilca, O., *et al.* Risk factors for community-acquired urinary tract infection caused by ESBL-producing bacteria in children. Pediatr Int, 2012. 54: 858.
https://www.ncbi.nlm.nih.gov/pubmed/22882781
369. Tratselas, A., *et al.* Outcome of urinary tract infections caused by extended spectrum beta-lactamase-producing Enterobacteriaceae in children. Pediatr Infect Dis J, 2011. 30: 707.
https://www.ncbi.nlm.nih.gov/pubmed/21248655
370. Naber, K.G., *et al.*, EAU/International Consultation on Urological Infections 2010, European Association of Urology: The Netherlands.
371. Montini, G., *et al.* Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. Pediatrics, 2008. 122: 1064.
https://www.ncbi.nlm.nih.gov/pubmed/18977988
372. Garin, E.H., *et al.* Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics, 2006. 117: 626.
https://www.ncbi.nlm.nih.gov/pubmed/16510640
373. Pennesi, M., *et al.* Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. Pediatrics, 2008. 121: e1489.
https://www.ncbi.nlm.nih.gov/pubmed/18490378
374. Roussey-Kesler, G., *et al.* Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. J Urol, 2008. 179: 674.
https://www.ncbi.nlm.nih.gov/pubmed/18082208

375. Hari, P., *et al.* Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med, 2014. 371: 1071.
https://www.ncbi.nlm.nih.gov/pubmed/25207775
376. Wang, H.H., *et al.* Efficacy of antibiotic prophylaxis in children with vesicoureteral reflux: systematic review and meta-analysis. J Urol, 2015. 193: 963.
https://www.ncbi.nlm.nih.gov/pubmed/25196653
377. Lee, S.J., *et al.* Probiotics prophylaxis in infants with primary vesicoureteral reflux. Pediatr Nephrol, 2015. 30: 609.
https://www.ncbi.nlm.nih.gov/pubmed/25354903
378. Salo, J., *et al.* Cranberry juice for the prevention of recurrences of urinary tract infections in children: a randomized placebo-controlled trial. Clin Infect Dis, 2012. 54: 340.
https://www.ncbi.nlm.nih.gov/pubmed/22100577
379. Afshar, K., *et al.* Cranberry juice for the prevention of pediatric urinary tract infection: a randomized controlled trial. J Urol, 2012. 188: 1584.
https://www.ncbi.nlm.nih.gov/pubmed/22910239
380. Schwenger, E.M., *et al.* Probiotics for preventing urinary tract infections in adults and children. Cochrane Database Syst Rev, 2015: CD008772.
https://www.ncbi.nlm.nih.gov/pubmed/26695595
381. Kotoula, A., *et al.* Comparative efficacies of procalcitonin and conventional inflammatory markers for prediction of renal parenchymal inflammation in pediatric first urinary tract infection. Urology, 2009. 73: 782.
https://www.ncbi.nlm.nih.gov/pubmed/19152962
382. Austin, P.F., *et al.* The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. Neurourol Urodyn, 2016. 35: 471.
https://www.ncbi.nlm.nih.gov/pubmed/25772695
383. Hellstrom, A.L., *et al.* Micturition habits and incontinence in 7-year-old Swedish school entrants. Eur J Pediatr, 1990. 149: 434.
https://www.ncbi.nlm.nih.gov/pubmed/2332015
384. Bakker, E., *et al.* Voiding habits and wetting in a population of 4,332 Belgian schoolchildren aged between 10 and 14 years. Scand J Urol Nephrol, 2002. 36: 354.
https://www.ncbi.nlm.nih.gov/pubmed/12487740
385. Soderstrom, U., *et al.* Urinary and faecal incontinence: a population-based study. Acta Paediatr, 2004. 93: 386.
https://www.ncbi.nlm.nih.gov/pubmed/15124844
386. Sureshkumar, P., *et al.* Daytime urinary incontinence in primary school children: a population-based survey. J Pediatr, 2000. 137: 814.
https://www.ncbi.nlm.nih.gov/pubmed/11113838
387. Sureshkumar, P., *et al.* A population based study of 2,856 school-age children with urinary incontinence. J Urol, 2009. 181: 808.
https://www.ncbi.nlm.nih.gov/pubmed/19110268
388. Veiga, M.L., *et al.* Constipation in children with isolated overactive bladders. J Pediatr Urol, 2013. 9: 945.
https://www.ncbi.nlm.nih.gov/pubmed/23462384
389. Borch, L., *et al.* Bladder and bowel dysfunction and the resolution of urinary incontinence with successful management of bowel symptoms in children. Acta Paediatr, 2013. 102: e215.
https://www.ncbi.nlm.nih.gov/pubmed/23368903
390. Chang, S.J., *et al.* Treatment of daytime urinary incontinence: A standardization document from the International Children's Continence Society. Neurourol Urodyn, 2015.
https://www.ncbi.nlm.nih.gov/pubmed/26473630
391. Hoebeke, P., *et al.* Diagnostic evaluation of children with daytime incontinence. J Urol, 2010. 183: 699.
https://www.ncbi.nlm.nih.gov/pubmed/20022025
392. Akbal, C., *et al.* Dysfunctional voiding and incontinence scoring system: quantitative evaluation of incontinence symptoms in pediatric population. J Urol, 2005. 173: 969.
https://www.ncbi.nlm.nih.gov/pubmed/15711352
393. Farhat, W., *et al.* The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children. J Urol, 2000. 164: 1011.
https://www.ncbi.nlm.nih.gov/pubmed/10958730

394. Chang, S.J., *et al.* Constipation is associated with incomplete bladder emptying in healthy children. Neurourol Urodyn, 2012. 31: 105.
https://www.ncbi.nlm.nih.gov/pubmed/22038844
395. Burgers, R.E., *et al.* Management of functional constipation in children with lower urinary tract symptoms: report from the Standardization Committee of the International Children's Continence Society. J Urol, 2013. 190: 29.
https://www.ncbi.nlm.nih.gov/pubmed/23313210
396. van Gool, J.D., *et al.* Multi-center randomized controlled trial of cognitive treatment, placebo, oxybutynin, bladder training, and pelvic floor training in children with functional urinary incontinence. Neurourol Urodyn, 2014. 33: 482.
https://www.ncbi.nlm.nih.gov/pubmed/23775924
397. Hellstrom, A.L. Urotherapy in children with dysfunctional bladder. Scand J Urol Nephrol Suppl, 1992. 141: 106.
https://www.ncbi.nlm.nih.gov/pubmed/1609245
398. Barroso, U., Jr., *et al.* Electrical stimulation for lower urinary tract dysfunction in children: a systematic review of the literature. Neurourol Urodyn, 2011. 30: 1429.
https://www.ncbi.nlm.nih.gov/pubmed/21717502
399. Bower, W.F., *et al.* A review of non-invasive electro neuromodulation as an intervention for non-neurogenic bladder dysfunction in children. Neurourol Urodyn, 2004. 23: 63.
https://www.ncbi.nlm.nih.gov/pubmed/14694460
400. De Paepe, H., *et al.* Pelvic-floor therapy in girls with recurrent urinary tract infections and dysfunctional voiding. Br J Urol, 1998. 81 Suppl 3: 109.
https://www.ncbi.nlm.nih.gov/pubmed/10792172
401. Vijverberg, M.A., *et al.* Bladder rehabilitation, the effect of a cognitive training programme on urge incontinence. Eur Urol, 1997. 31: 68.
https://www.ncbi.nlm.nih.gov/pubmed/9032538
402. Lordelo, P., *et al.* Prospective study of transcutaneous parasacral electrical stimulation for overactive bladder in children: long-term results. J Urol, 2009. 182: 2900.
https://www.ncbi.nlm.nih.gov/pubmed/19846164
403. Ladi-Seyedian, S., *et al.* Management of non-neuropathic underactive bladder in children with voiding dysfunction by animated biofeedback: a randomized clinical trial. Urology, 2015. 85: 205.
https://www.ncbi.nlm.nih.gov/pubmed/25444633
404. Kajbafzadeh, A.M., *et al.* Transcutaneous interferential electrical stimulation for the management of non-neuropathic underactive bladder in children: a randomised clinical trial. BJU Int, 2016. 117: 793.
https://www.ncbi.nlm.nih.gov/pubmed/26086897
405. Featherstone, N., *et al.* Ephedrine hydrochloride: novel use in the management of resistant non-neurogenic daytime urinary incontinence in children. J Pediatr Urol, 2013. 9: 915.
https://www.ncbi.nlm.nih.gov/pubmed/23332206
406. Nijman, R.J., *et al.* Tolterodine treatment for children with symptoms of urinary urge incontinence suggestive of detrusor overactivity: results from 2 randomized, placebo controlled trials. J Urol, 2005. 173: 1334.
https://www.ncbi.nlm.nih.gov/pubmed/15758796
407. Marschall-Kehrel, D., *et al.* Treatment with propiverine in children suffering from nonneurogenic overactive bladder and urinary incontinence: results of a randomized placebo-controlled phase 3 clinical trial. Eur Urol, 2009. 55: 729.
https://www.ncbi.nlm.nih.gov/pubmed/18502028
408. Kramer, S.A., *et al.* Double-blind placebo controlled study of alpha-adrenergic receptor antagonists (doxazosin) for treatment of voiding dysfunction in the pediatric population. J Urol, 2005. 173: 2121.
https://www.ncbi.nlm.nih.gov/pubmed/15879863
409. Hoebeke, P., *et al.* The effect of botulinum-A toxin in incontinent children with therapy resistant overactive detrusor. J Urol, 2006. 176: 328.
https://www.ncbi.nlm.nih.gov/pubmed/16753434
410. Groen, L.A., *et al.* Sacral neuromodulation with an implantable pulse generator in children with lower urinary tract symptoms: 15-year experience. J Urol, 2012. 188: 1313.
https://www.ncbi.nlm.nih.gov/pubmed/22902022
411. Lackgren, G., *et al.* Nocturnal enuresis: a suggestion for a European treatment strategy. Acta Paediatr, 1999. 88: 679.
https://www.ncbi.nlm.nih.gov/pubmed/10419258

412. Neveus, T., *et al.* The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol, 2006. 176: 314.
https://www.ncbi.nlm.nih.gov/pubmed/16753432
413. Neveus, T., *et al.* Enuresis--background and treatment. Scand J Urol Nephrol Suppl, 2000: 1.
https://www.ncbi.nlm.nih.gov/pubmed/11196246
414. Negoro, H., *et al.* Chronobiology of micturition: putative role of the circadian clock. J Urol, 2013. 190: 843.
https://www.ncbi.nlm.nih.gov/pubmed/23429068
415. Hjalmas, K., *et al.* Nocturnal enuresis: an international evidence based management strategy. J Urol, 2004. 171: 2545.
https://www.ncbi.nlm.nih.gov/pubmed/10419258
416. Caldwell, P.H., *et al.* Simple behavioural interventions for nocturnal enuresis in children. Cochrane Database Syst Rev, 2013. 7: CD003637.
https://www.ncbi.nlm.nih.gov/pubmed/23881652
417. Glazener, C.M., *et al.* Alarm interventions for nocturnal enuresis in children. Cochrane Database Syst Rev, 2005: CD002911.
https://www.ncbi.nlm.nih.gov/pubmed/15846643
418. Dehoorne, J.L., *et al.* Desmopressin toxicity due to prolonged half-life in 18 patients with nocturnal enuresis. J Urol, 2006. 176: 754.
https://www.ncbi.nlm.nih.gov/pubmed/16813936
419. Glazener, C.M., *et al.* Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev, 2002: CD002112.
https://www.ncbi.nlm.nih.gov/pubmed/12137645
420. Gokce, M.I., *et al.* Does structured withdrawal of desmopressin improve relapse rates in patients with monosymptomatic enuresis? J Urol, 2014. 192: 530.
https://www.ncbi.nlm.nih.gov/pubmed/24518770
421. Glazener, C.M., *et al.* Tricyclic and related drugs for nocturnal enuresis in children. Cochrane Database Syst Rev, 2003: CD002117.
https://www.ncbi.nlm.nih.gov/pubmed/12917922
422. Bauer, S.B. The management of the myelodysplastic child: a paradigm shift. BJU Int, 2003. 92 Suppl 1: 23.
https://www.ncbi.nlm.nih.gov/pubmed/
423. Lapides, J., *et al.* Clean, intermittent self-catheterization in the treatment of urinary tract disease. 1972. J Urol, 2002. 167: 1131.
https://www.ncbi.nlm.nih.gov/pubmed/
424. Retik, A.B., *et al.* Cutaneous ureteroileostomy in children. N Engl J Med, 1967. 277: 217.
https://www.ncbi.nlm.nih.gov/pubmed/
425. Bauer, S.B., The management of spina bifida from birth onwards., in Paediatric urology, R.H. Whitaker & J.R. Woodard, Eds. 1985, Butterworths: London.
426. Bauer, S.B., Early evaluation and management of children with spina bifida., in Urologic surgery in neonates and young infants., L.R. King, Editor. 1988, WB Saunders: Philadelphia.
427. Hunt, G.M., *et al.* The pattern of congenital renal anomalies associated with neural-tube defects. Dev Med Child Neurol, 1987. 29: 91.
https://www.ncbi.nlm.nih.gov/pubmed/3556803
428. Wilcock, A.R., *et al.* Deformities of the renal tract in children with meningomyelocele and hydrocephalus, compared with those of children showing no such central nervous system deformities. Br J Urol, 1970. 42: 152.
https://www.ncbi.nlm.nih.gov/pubmed/5420153
429. Pierre-Kahn, A., *et al.* Congenital lumbosacral lipomas. Childs Nerv Syst, 1997. 13: 298.
https://www.ncbi.nlm.nih.gov/pubmed/9272285
430. Aoki, H., *et al.* [Evaluation of neurogenic bladder in patients with spinal cord injury using a CMG. EMG study and CMG.UFM.EMG study]. Hinyokika Kiyo, 1985. 31: 937.
https://www.ncbi.nlm.nih.gov/pubmed/4061211
431. Bradley, C.S., *et al.* Urodynamic evaluation of the bladder and pelvic floor. Gastroenterol Clin North Am, 2008. 37: 539.
https://www.ncbi.nlm.nih.gov/pubmed/18793995
432. Casado, J.S., *et al.* [Urodynamic assessment of the voiding phase in childhood]. Arch Esp Urol, 2002. 55: 177.
https://www.ncbi.nlm.nih.gov/pubmed/12014050

433. Wen, J.G., *et al.* Cystometry techniques in female infants and children. Int Urogynecol J Pelvic Floor Dysfunct, 2000. 11: 103.
https://www.ncbi.nlm.nih.gov/pubmed/10805268
434. Norgaard, J.P., *et al.* Standardization and definitions in lower urinary tract dysfunction in children. International Children's Continence Society. Br J Urol, 1998. 81 Suppl 3: 1.
https://www.ncbi.nlm.nih.gov/pubmed/9634012
435. Agarwal, S.K., *et al.* Urodynamic correlates of resolution of reflux in meningomyelocele patients. J Urol, 1997. 158: 580.
https://www.ncbi.nlm.nih.gov/pubmed/9224367
436. Ghoniem, G.M., *et al.* The value of leak pressure and bladder compliance in the urodynamic evaluation of meningomyelocele patients. J Urol, 1990. 144: 1440.
https://www.ncbi.nlm.nih.gov/pubmed/2231938
437. Ghoniem, G.M., *et al.* Detrusor properties in myelomeningocele patients: in vitro study. J Urol, 1998. 159: 2193.
https://www.ncbi.nlm.nih.gov/pubmed/9598568
438. Palmer, L.S., *et al.* Age related bladder capacity and bladder capacity growth in children with myelomeningocele. J Urol, 1997. 158: 1261.
https://www.ncbi.nlm.nih.gov/pubmed/9258190
439. Tanikaze, S., *et al.* [Cystometric examination for neurogenic bladder of neonates and infants]. Hinyokika Kiyo, 1991. 37: 1403.
https://www.ncbi.nlm.nih.gov/pubmed/1767767
440. Zoller, G., *et al.* Pre- and postoperative urodynamic findings in children with tethered spinal cord syndrome. Eur Urol, 1991. 19: 139.
https://www.ncbi.nlm.nih.gov/pubmed/2022217
441. Webb, R.J., *et al.* Measurement of voiding pressures on ambulatory monitoring: comparison with conventional cystometry. Br J Urol, 1990. 65: 152.
https://www.ncbi.nlm.nih.gov/pubmed/2317646
442. Zermann, D.H., *et al.* Diagnostic value of natural fill cystometry in neurogenic bladder in children. Eur Urol, 1997. 32: 223.
https://www.ncbi.nlm.nih.gov/pubmed/9286658
443. McInerney, P.D., *et al.* Ambulatory urodynamics. Br J Urol, 1991. 67: 272.
https://www.ncbi.nlm.nih.gov/pubmed/2021814
444. Yeung, C.K., *et al.* Natural filling cystometry in infants and children. Br J Urol, 1995. 75: 531.
https://www.ncbi.nlm.nih.gov/pubmed/7788266
445. Swithinbank, L.V., *et al.* Role of ambulatory urodynamic monitoring in clinical urological practice. Neurourol Urodyn, 1999. 18: 215.
https://www.ncbi.nlm.nih.gov/pubmed/10338442
446. Rodriguez-Ruiz, M., *et al.* Study of kidney damage in paediatric patients with neurogenic bladder and its relationship with the pattern of bladder function and treatment received. Actas Urol Esp, 2016. 40: 37.
https://www.ncbi.nlm.nih.gov/pubmed/26183019
447. McGuire, E.J., *et al.* Prognostic value of urodynamic testing in myelodysplastic patients. 1981. J Urol, 2002. 167: 1049.
https://www.ncbi.nlm.nih.gov/pubmed/11905876
448. Sillen, U., *et al.* Development of the urodynamic pattern in infants with myelomeningocele. Br J Urol, 1996. 78: 596.
https://www.ncbi.nlm.nih.gov/pubmed/8944517
449. Tarcan, T., *et al.* Long-term followup of newborns with myelodysplasia and normal urodynamic findings: Is followup necessary? J Urol, 2001. 165: 564.
https://www.ncbi.nlm.nih.gov/pubmed/11176436
450. Bauer, S.B. The argument for early assessment and treatment of infants with spina bifida Dialogues Pediatr Urol 2000. 23: 2.
451. Kaefer, M., *et al.* Improved bladder function after prophylactic treatment of the high risk neurogenic bladder in newborns with myelomentingocele. J Urol, 1999. 162: 1068.
https://www.ncbi.nlm.nih.gov/pubmed/10458433
452. Kasabian, N.G., *et al.* The prophylactic value of clean intermittent catheterization and anticholinergic medication in newborns and infants with myelodysplasia at risk of developing urinary tract deterioration. Am J Dis Child, 1992. 146: 840.
https://www.ncbi.nlm.nih.gov/pubmed/1496955

453. Kaufman, A.M., *et al.* Decreased bladder compliance in patients with myelomeningocele treated with radiological observation. J Urol, 1996. 156: 2031.
https://www.ncbi.nlm.nih.gov/pubmed/8965337
454. Lin-Dyken, D.C., *et al.* Follow-up of clean intermittent catheterization for children with neurogenic bladders. Urology, 1992. 40: 525.
https://www.ncbi.nlm.nih.gov/pubmed/1466106
455. Wang, S.C., *et al.* Urethral dilation in the management of urological complications of myelodysplasia. J Urol, 1989. 142: 1054.
https://www.ncbi.nlm.nih.gov/pubmed/2795730
456. Wu, H.Y., *et al.* Neurogenic bladder dysfunction due to myelomeningocele: neonatal versus childhood treatment. J Urol, 1997. 157: 2295.
https://www.ncbi.nlm.nih.gov/pubmed/9146656
457. Park, J.M. Early reduction of mechanical load of the bladder improves compliance: experimental and clinical observations. Dialogues Pediatr Urol 2000. 23: 6.
458. Joseph, D.B., *et al.* Clean, intermittent catheterization of infants with neurogenic bladder. Pediatrics, 1989. 84: 78.
https://www.ncbi.nlm.nih.gov/pubmed/2740179
459. Lindehall, B., *et al.* Long-term intermittent catheterization: the experience of teenagers and young adults with myelomeningocele. J Urol, 1994. 152: 187.
https://www.ncbi.nlm.nih.gov/pubmed/8201663
460. Baskin, L.S., *et al.* Treatment of infants with neurogenic bladder dysfunction using anticholinergic drugs and intermittent catheterisation. Br J Urol, 1990. 66: 532.
https://www.ncbi.nlm.nih.gov/pubmed/2249125
461. Connor, J.P., *et al.* Early cystometrograms can predict the response to intravesical instillation of oxybutynin chloride in myelomeningocele patients. J Urol, 1994. 151: 1045.
https://www.ncbi.nlm.nih.gov/pubmed/8126787
462. Ellsworth, P.I., *et al.* Use of tolterodine in children with neurogenic detrusor overactivity: relationship between dose and urodynamic response. J Urol, 2005. 174: 1647.
https://www.ncbi.nlm.nih.gov/pubmed/16148673
463. Ferrara, P., *et al.* Side-effects of oral or intravesical oxybutynin chloride in children with spina bifida. BJU Int, 2001. 87: 674.
https://www.ncbi.nlm.nih.gov/pubmed/11350411
464. Franco, I. Overactive bladder in children. Part 2: Management. J Urol, 2007. 178: 769.
https://www.ncbi.nlm.nih.gov/pubmed/17631323
465. Goessl, C., *et al.* Urodynamic effects of oral oxybutynin chloride in children with myelomeningocele and detrusor hyperreflexia. Urology, 1998. 51: 94.
https://www.ncbi.nlm.nih.gov/pubmed/9457296
466. Haferkamp, A., *et al.* Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients. Spinal Cord, 2000. 38: 250.
https://www.ncbi.nlm.nih.gov/pubmed/10822396
467. Mahanta, K., *et al.* Comparative efficacy and safety of extended-release and instant-release tolterodine in children with neural tube defects having cystometric abnormalities. J Pediatr Urol, 2008. 4: 118.
https://www.ncbi.nlm.nih.gov/pubmed/18631906
468. Austin, P.F., *et al.* Alpha-adrenergic blockade in children with neuropathic and nonneuropathic voiding dysfunction. J Urol, 1999. 162: 1064.
https://www.ncbi.nlm.nih.gov/pubmed/10458432
469. Deshpande, A.V., *et al.* Study of botulinum toxin A in neurogenic bladder due to spina bifida in children. ANZ J Surg, 2010. 80: 250.
https://www.ncbi.nlm.nih.gov/pubmed/20575951
470. Game, X., *et al.* Botulinum toxin-A (Botox) intradetrusor injections in children with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. J Pediatr Urol, 2009. 5: 156.
https://www.ncbi.nlm.nih.gov/pubmed/19264554
471. Mangera, A., *et al.* Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). Eur Urol, 2011. 60: 784.
https://www.ncbi.nlm.nih.gov/pubmed/21782318

472. Schulte-Baukloh, H., *et al.* Repeated botulinum-A toxin injections in treatment of children with neurogenic detrusor overactivity. Urology, 2005. 66: 865.
https://www.ncbi.nlm.nih.gov/pubmed/16230156
473. Schulte-Baukloh, H., *et al.* Botulinum-A toxin in the treatment of neurogenic bladder in children. Pediatrics, 2002. 110: 420.
https://www.ncbi.nlm.nih.gov/pubmed/12814690
474. Leippold, T., *et al.* Botulinum toxin as a new therapy option for voiding disorders: current state of the art. Eur Urol, 2003. 44: 165.
https://www.ncbi.nlm.nih.gov/pubmed/12875934
475. Lusuardi, L., *et al.* [Minimally invasive, safe treatment of the neurogenic bladder with botulinum-A-toxin in children with myelomeningocele]. Aktuelle Urol, 2004. 35: 49.
https://www.ncbi.nlm.nih.gov/pubmed/14997415
476. Schroder, A., *et al.* New strategies for medical management of overactive bladder in children. Curr Opin Urol, 2010. 20: 313.
https://www.ncbi.nlm.nih.gov/pubmed/21475074
477. Schurch, B., *et al.* Botulinum toxin injections for paediatric incontinence. Curr Opin Urol, 2005. 15: 264.
https://www.ncbi.nlm.nih.gov/pubmed/15928517
478. Smith, C.P., *et al.* Emerging role of botulinum toxin in the treatment of neurogenic and non-neurogenic voiding dysfunction. Curr Urol Rep, 2002. 3: 382.
https://www.ncbi.nlm.nih.gov/pubmed/12354347
479. Akbar, M., *et al.* Repeated botulinum-A toxin injections in the treatment of myelodysplastic children and patients with spinal cord injuries with neurogenic bladder dysfunction. BJU Int, 2007. 100: 639.
https://www.ncbi.nlm.nih.gov/pubmed/17532858
480. DasGupta, R., *et al.* Botulinum toxin in paediatric urology: a systematic literature review. Pediatr Surg Int, 2009. 25: 19.
https://www.ncbi.nlm.nih.gov/pubmed/18953547
481. Kajbafzadeh, A.M., *et al.* Intravesical injection of botulinum toxin type A: management of neuropathic bladder and bowel dysfunction in children with myelomeningocele. Urology, 2006. 68: 1091.
https://www.ncbi.nlm.nih.gov/pubmed/17113899
482. Franco, I., *et al.* The use of botulinum toxin A injection for the management of external sphincter dyssynergia in neurologically normal children. J Urol, 2007. 178: 1775.
https://www.ncbi.nlm.nih.gov/pubmed/17707430
483. Mokhless, I., *et al.* Botulinum A toxin urethral sphincter injection in children with nonneurogenic neurogenic bladder. J Urol, 2006. 176: 1767.
https://www.ncbi.nlm.nih.gov/pubmed/16945643
484. Younoszai, M.K. Stooling problems in patients with myelomeningocele. South Med J, 1992. 85: 718.
https://www.ncbi.nlm.nih.gov/pubmed/1631686
485. Aksnes, G., *et al.* Appendicostomy for antegrade enema: effects on somatic and psychosocial functioning in children with myelomeningocele. Pediatrics, 2002. 109: 484.
https://www.ncbi.nlm.nih.gov/pubmed/11875145
486. Krogh, K., *et al.* [Treatment of anal incontinence and constipation with transanal irrigation]. Ugeskr Laeger, 1999. 161: 253.
https://www.ncbi.nlm.nih.gov/pubmed/10025223
487. Squire, R., *et al.* The clinical application of the Malone antegrade colonic enema. J Pediatr Surg, 1993. 28: 1012.
https://www.ncbi.nlm.nih.gov/pubmed/8229586
488. Van Savage, J.G., *et al.* Laparoscopic antegrade continence enema in situ appendix procedure for refractory constipation and overflow fecal incontinence in children with spina bifida. J Urol, 2000. 164: 1084.
https://www.ncbi.nlm.nih.gov/pubmed/10958747
489. Whitehead, W.E., *et al.* Treatment options for fecal incontinence. Dis Colon Rectum, 2001. 44: 131.
https://www.ncbi.nlm.nih.gov/pubmed/11805574
490. Loening-Baucke, V., *et al.* Biofeedback training for patients with myelomeningocele and fecal incontinence. Dev Med Child Neurol, 1988. 30: 781.
https://www.ncbi.nlm.nih.gov/pubmed/3234607

491. Marshall, D.F., *et al.* Altered bladder and bowel function following cutaneous electrical field stimulation in children with spina bifida--interim results of a randomized double-blind placebo-controlled trial. Eur J Pediatr Surg, 1997. 7 Suppl 1: 41.
https://www.ncbi.nlm.nih.gov/pubmed/9497117
492. Hansson, S., *et al.* Untreated asymptomatic bacteriuria in girls: I--Stability of urinary isolates. Bmj, 1989. 298: 853.
https://www.ncbi.nlm.nih.gov/pubmed/2497822
493. Hansson, S., *et al.* Untreated bacteriuria in asymptomatic girls with renal scarring. Pediatrics, 1989. 84: 964.
https://www.ncbi.nlm.nih.gov/pubmed/2587151
494. Hansson, S., *et al.* Untreated asymptomatic bacteriuria in girls: II--Effect of phenoxymethylpenicillin and erythromycin given for intercurrent infections. Bmj, 1989. 298: 856.
https://www.ncbi.nlm.nih.gov/pubmed/2497823
495. Johnson, H.W., *et al.* A short-term study of nitrofurantoin prophylaxis in children managed with clean intermittent catheterization. Pediatrics, 1994. 93: 752.
https://www.ncbi.nlm.nih.gov/pubmed/8165073
496. Schlager, T.A., *et al.* Nitrofurantoin prophylaxis for bacteriuria and urinary tract infection in children with neurogenic bladder on intermittent catheterization. J Pediatr, 1998. 132: 704.
https://www.ncbi.nlm.nih.gov/pubmed/9580774
497. Nguyen, D.H., *et al.* Gastric bladder reconstruction. Urol Clin North Am, 1991. 18: 649.
https://www.ncbi.nlm.nih.gov/pubmed/1949398
498. Bandi, G., *et al.* Comparison of traditional enterocystoplasty and seromuscular colocystoplasty lined with urothelium. J Pediatr Urol, 2007. 3: 484.
https://www.ncbi.nlm.nih.gov/pubmed/18947800
499. Duel, B.P., *et al.* Alternative techniques for augmentation cystoplasty. J Urol, 1998. 159: 998.
https://www.ncbi.nlm.nih.gov/pubmed/9474216
500. Austin, P.F., *et al.* Advantages of rectus fascial slings for urinary incontinence in children with neuropathic bladders. J Urol, 2001. 165: 2369.
https://www.ncbi.nlm.nih.gov/pubmed/11398778
501. Guys, J.M., *et al.* Endoscopic treatment of urinary incontinence: long-term evaluation of the results. J Urol, 2001. 165: 2389.
https://www.ncbi.nlm.nih.gov/pubmed/11371983
502. Holmes, N.M., *et al.* Placement of artificial urinary sphincter in children and simultaneous gastrocystoplasty. J Urol, 2001. 165: 2366.
https://www.ncbi.nlm.nih.gov/pubmed/11371944
503. Kassouf, W., *et al.* Collagen injection for treatment of urinary incontinence in children. J Urol, 2001. 165: 1666.
https://www.ncbi.nlm.nih.gov/pubmed/11342951
504. Kryger, J.V., *et al.* Long-term results of artificial urinary sphincters in children are independent of age at implantation. J Urol, 2001. 165: 2377.
https://www.ncbi.nlm.nih.gov/pubmed/11371981
505. Naglo, A.S. Continence training of children with neurogenic bladder and detrusor hyperactivity: effect of atropine. Scand J Urol Nephrol, 1982. 16: 211.
https://www.ncbi.nlm.nih.gov/pubmed/7163785
506. Herndon, C.D., *et al.* The Indiana experience with artificial urinary sphincters in children and young adults. J Urol, 2003. 169: 650.
https://www.ncbi.nlm.nih.gov/pubmed/12544336
507. Medel, R., *et al.* Urinary continence outcome after augmentation ileocystoplasty as a single surgical procedure in patients with myelodysplasia. J Urol, 2002. 168: 1849.
https://www.ncbi.nlm.nih.gov/pubmed/12352374
508. Mitchell, M.E., *et al.* Intestinocystoplasty and total bladder replacement in children and young adults: followup in 129 cases. J Urol, 1987. 138: 579.
https://www.ncbi.nlm.nih.gov/pubmed/3625861
509. Shekarriz, B., *et al.* Surgical complications of bladder augmentation: comparison between various enterocystoplasties in 133 patients. Urology, 2000. 55: 123.
https://www.ncbi.nlm.nih.gov/pubmed/10654908
510. Balachandra, B., *et al.* Adenocarcinoma arising in a gastrocystoplasty. J Clin Pathol, 2007. 60: 85.
https://www.ncbi.nlm.nih.gov/pubmed/17213351
511. Castellan, M., *et al.* Tumor in bladder reservoir after gastrocystoplasty. J Urol, 2007. 178: 1771.
https://www.ncbi.nlm.nih.gov/pubmed/17707009

512. Husmann, D.A., *et al.* Long-term follow up of enteric bladder augmentations: the risk for malignancy. J Pediatr Urol, 2008. 4: 381.
https://www.ncbi.nlm.nih.gov/pubmed/18653384
513. Soergel, T.M., *et al.* Transitional cell carcinoma of the bladder following augmentation cystoplasty for the neuropathic bladder. J Urol, 2004. 172: 1649.
https://www.ncbi.nlm.nih.gov/pubmed/15371782
514. Sung, M.T., *et al.* Urothelial carcinoma following augmentation cystoplasty: an aggressive variant with distinct clinicopathological characteristics and molecular genetic alterations. Histopathology, 2009. 55: 161.
https://www.ncbi.nlm.nih.gov/pubmed/19694823
515. Vemulakonda, V.M., *et al.* Metastatic adenocarcinoma after augmentation gastrocystoplasty. J Urol, 2008. 179: 1094.
https://www.ncbi.nlm.nih.gov/pubmed/18206936
516. Lebowitz, R.L., *et al.* Neonatal hydronephrosis: 146 cases. Radiol Clin North Am, 1977. 15: 49.
https://www.ncbi.nlm.nih.gov/pubmed/139634
517. Brown, T., *et al.* Neonatal hydronephrosis in the era of sonography. AJR Am J Roentgenol, 1987. 148: 959.
https://www.ncbi.nlm.nih.gov/pubmed/3034009
518. Koff, S.A. Problematic ureteropelvic junction obstruction. J Urol, 1987. 138: 390.
https://www.ncbi.nlm.nih.gov/pubmed/3599261
519. Gunn, T.R., *et al.* Antenatal diagnosis of urinary tract abnormalities by ultrasonography after 28 weeks' gestation: incidence and outcome. Am J Obstet Gynecol, 1995. 172: 479.
https://www.ncbi.nlm.nih.gov/pubmed/7856673
520. Grignon, A., *et al.* Ureteropelvic junction stenosis: antenatal ultrasonographic diagnosis, postnatal investigation, and follow-up. Radiology, 1986. 160: 649.
https://www.ncbi.nlm.nih.gov/pubmed/3526403
521. Flashner, S.C., *et al.*, Ureteropelvic junction, in Clinical Pediatric Urology. 1976, WB Saunders: Philadelphia.
522. Thomas, D.F. Prenatally detected uropathy: epidemiological considerations. Br J Urol, 1998. 81 Suppl 2: 8.
https://www.ncbi.nlm.nih.gov/pubmed/9602790
523. Ebel, K.D. Uroradiology in the fetus and newborn: diagnosis and follow-up of congenital obstruction of the urinary tract. Pediatr Radiol, 1998. 28: 630.
https://www.ncbi.nlm.nih.gov/pubmed/9716640
524. O'Reilly, P., *et al.* Consensus on diuresis renography for investigating the dilated upper urinary tract. Radionuclides in Nephrourology Group. Consensus Committee on Diuresis Renography. J Nucl Med, 1996. 37: 1872.
https://www.ncbi.nlm.nih.gov/pubmed/8917195
525. Choong, K.K., *et al.* Volume expanded diuretic renography in the postnatal assessment of suspected uretero-pelvic junction obstruction. J Nucl Med, 1992. 33: 2094.
https://www.ncbi.nlm.nih.gov/pubmed/1460498
526. Reddy, P.P., *et al.* Prenatal diagnosis. Therapeutic implications. Urol Clin North Am, 1998. 25: 171.
https://www.ncbi.nlm.nih.gov/pubmed/9633572
527. Braga, L.H., *et al.* Pilot randomized, placebo controlled trial to investigate the effect of antibiotic prophylaxis on the rate of urinary tract infection in infants with prenatal hydronephrosis. J Urol, 2014. 191: 1501.
https://www.ncbi.nlm.nih.gov/pubmed/24679865
528. Craig, J., *et al.*, Long-term antibiotics to prevent urinary tract infection in children with isolated vesicoureteric reflux: a placebo-controlled randomized trial., in Australian and New Zeland Society of Nephrology 38th Annual Scientific Meeting 2002: Sydney.
529. Novick, A.C., *et al.*, Surgery of the kidney, in Campell's Urology. 1998, WB Saunders: Philadelphia.
530. Fernbach, S.K., *et al.* Ultrasound grading of hydronephrosis: introduction to the system used by the Society for Fetal Urology. Pediatr Radiol, 1993. 23: 478.
https://www.ncbi.nlm.nih.gov/pubmed/8255658
531. Tasian, G.E., *et al.* The robotic-assisted laparoscopic pyeloplasty: gateway to advanced reconstruction. Urol Clin North Am, 2015. 42: 89.
https://www.ncbi.nlm.nih.gov/pubmed/25455175
532. Reddy, M.N., *et al.* The laparoscopic pyeloplasty: is there a role in the age of robotics? Urol Clin North Am, 2015. 42: 43.
https://www.ncbi.nlm.nih.gov/pubmed/25455171

533. Huang, Y., *et al.* An updated meta-analysis of laparoscopic versus open pyeloplasty for ureteropelvic junction obstruction in children. Int J Clin Exp Med, 2015. 8: 4922.
https://www.ncbi.nlm.nih.gov/pubmed/26131065
534. Trevisani, L.F., *et al.* Current controversies in pediatric urologic robotic surgery. Curr Opin Urol, 2013. 23: 72.
https://www.ncbi.nlm.nih.gov/pubmed/23169150
535. Cundy, T.P., *et al.* Meta-analysis of robot-assisted vs conventional laparoscopic and open pyeloplasty in children. BJU Int, 2014. 114: 582.
https://www.ncbi.nlm.nih.gov/pubmed/25383399
536. Arena, F., *et al.* Conservative treatment in primary neonatal megaureter. Eur J Pediatr Surg, 1998. 8: 347.
https://www.ncbi.nlm.nih.gov/pubmed/9926303
537. Peters, C.A., *et al.* Congenital obstructed megaureters in early infancy: diagnosis and treatment. J Urol, 1989. 142: 641.
https://www.ncbi.nlm.nih.gov/pubmed/2746792
538. Onen, A., *et al.* Long-term followup of prenatally detected severe bilateral newborn hydronephrosis initially managed nonoperatively. J Urol, 2002. 168: 1118.
https://www.ncbi.nlm.nih.gov/pubmed/12187248
539. Shukla, A.R., *et al.* Prenatally detected primary megaureter: a role for extended followup. J Urol, 2005. 173: 1353.
https://www.ncbi.nlm.nih.gov/pubmed/15758800
540. Sripathi, V., et al. Primary obstructive megaureter. J Pediatr Surg, 1991. 26: 826.
https://www.ncbi.nlm.nih.gov/pubmed/1895193
541. Fanos, V., *et al.* Antibiotics or surgery for vesicoureteric reflux in children. Lancet, 2004. 364: 1720.
https://www.ncbi.nlm.nih.gov/pubmed/15530633
542. Sargent, M.A. What is the normal prevalence of vesicoureteral reflux? Pediatr Radiol, 2000. 30: 587.
https://www.ncbi.nlm.nih.gov/pubmed/11009294
543. Skoog, S.J., *et al.* Pediatric Vesicoureteral Reflux Guidelines Panel Summary Report: Clinical Practice Guidelines for Screening Siblings of Children With Vesicoureteral Reflux and Neonates/ Infants With Prenatal Hydronephrosis. J Urol, 2010. 184: 1145.
https://www.ncbi.nlm.nih.gov/pubmed/20650494
544. Estrada, C.R., Jr., *et al.* Nomograms for predicting annual resolution rate of primary vesicoureteral reflux: results from 2,462 children. J Urol, 2009. 182: 1535.
https://www.ncbi.nlm.nih.gov/pubmed/19683762
545. Pirker, M.E., *et al.* Renal scarring in familial vesicoureteral reflux: is prevention possible? J Urol, 2006. 176: 1842.
https://www.ncbi.nlm.nih.gov/pubmed/16945668
546. Pirker, M.E., *et al.* Familial vesicoureteral reflux: influence of sex on prevalence and expression. J Urol, 2006. 176: 1776.
https://www.ncbi.nlm.nih.gov/pubmed/16945647
547. Hannula, A., *et al.* Vesicoureteral reflux in children with suspected and proven urinary tract infection. Pediatr Nephrol, 2010. 25: 1463.
https://www.ncbi.nlm.nih.gov/pubmed/20467791
548. Menezes, M., *et al.* Familial vesicoureteral reflux--is screening beneficial? J Urol, 2009. 182: 1673.
https://www.ncbi.nlm.nih.gov/pubmed/19692047
549. Alsaywid, B.S., *et al.* High grade primary vesicoureteral reflux in boys: long-term results of a prospective cohort study. J Urol, 2010. 184: 1598.
https://www.ncbi.nlm.nih.gov/pubmed/20728178
550. Noe, H.N. The long-term results of prospective sibling reflux screening. J Urol, 1992. 148: 1739.
https://www.ncbi.nlm.nih.gov/pubmed/1433599
551. Ural, Z., *et al.* Bladder dynamics and vesicoureteral reflux: factors associated with idiopathic lower urinary tract dysfunction in children. J Urol, 2008. 179: 1564.
https://www.ncbi.nlm.nih.gov/pubmed/18295262
552. Sillen, U., *et al.* The Swedish reflux trial in children: v. Bladder dysfunction. J Urol, 2010. 184: 298.
https://www.ncbi.nlm.nih.gov/pubmed/20488469
553. Sjostrom, S., *et al.* Spontaneous resolution of high grade infantile vesicoureteral reflux. J Urol, 2004. 172: 694.
https://www.ncbi.nlm.nih.gov/pubmed/15247764

554. Esbjorner, E., *et al.* Management of children with dilating vesico-ureteric reflux in Sweden. Acta Paediatr, 2004. 93: 37.
https://www.ncbi.nlm.nih.gov/pubmed/14989437
555. Knudson, M.J., *et al.* Predictive factors of early spontaneous resolution in children with primary vesicoureteral reflux. J Urol, 2007. 178: 1684.
https://www.ncbi.nlm.nih.gov/pubmed/17707023
556. Sjostrom, S., *et al.* Predictive factors for resolution of congenital high grade vesicoureteral reflux in infants: results of univariate and multivariate analyses. J Urol, 2010. 183: 1177.
https://www.ncbi.nlm.nih.gov/pubmed/20096864
557. Yeung, C.K., *et al.* Renal and bladder functional status at diagnosis as predictive factors for the outcome of primary vesicoureteral reflux in children. J Urol, 2006. 176: 1152.
https://www.ncbi.nlm.nih.gov/pubmed/16890714
558. Mohanan, N., *et al.* Renal parenchymal damage in intermediate and high grade infantile vesicoureteral reflux. J Urol, 2008. 180: 1635.
https://www.ncbi.nlm.nih.gov/pubmed/18708232
559. Olbing, H., *et al.* New renal scars in children with severe VUR: a 10-year study of randomized treatment. Pediatr Nephrol, 2003. 18: 1128.
https://www.ncbi.nlm.nih.gov/pubmed/14523634
560. Peters, C., *et al.* Vesicoureteral reflux associated renal damage: congenital reflux nephropathy and acquired renal scarring. J Urol, 2010. 184: 265.
https://www.ncbi.nlm.nih.gov/pubmed/20483150
561. Coplen, D.E., *et al.* Correlation of prenatal and postnatal ultrasound findings with the incidence of vesicoureteral reflux in children with fetal renal pelvic dilatation. J Urol, 2008. 180: 1631.
https://www.ncbi.nlm.nih.gov/pubmed/18718617
562. Estrada, C.R., *et al.* Vesicoureteral reflux and urinary tract infection in children with a history of prenatal hydronephrosis--should voiding cystourethrography be performed in cases of postnatally persistent grade II hydronephrosis? J Urol, 2009. 181: 801.
https://www.ncbi.nlm.nih.gov/pubmed/19095265
563. Lee, R.S., *et al.* Antenatal hydronephrosis as a predictor of postnatal outcome: a meta-analysis. Pediatrics, 2006. 118: 586.
https://www.ncbi.nlm.nih.gov/pubmed/16882811
564. Mallik, M., *et al.* Antenatally detected urinary tract abnormalities: more detection but less action. Pediatr Nephrol, 2008. 23: 897.
https://www.ncbi.nlm.nih.gov/pubmed/18278521
565. Phan, V., *et al.* Vesicoureteral reflux in infants with isolated antenatal hydronephrosis. Pediatr Nephrol, 2003. 18: 1224.
https://www.ncbi.nlm.nih.gov/pubmed/14586679
566. Ylinen, E., *et al.* Risk of renal scarring in vesicoureteral reflux detected either antenatally or during the neonatal period. Urology, 2003. 61: 1238.
https://www.ncbi.nlm.nih.gov/pubmed/12809909
567. Leonardo, C.R., *et al.* Risk factors for renal scarring in children and adolescents with lower urinary tract dysfunction. Pediatr Nephrol, 2007. 22: 1891.
https://www.ncbi.nlm.nih.gov/pubmed/17874252
568. Naseer, S.R., *et al.* New renal scars in children with urinary tract infections, vesicoureteral reflux and voiding dysfunction: a prospective evaluation. J Urol, 1997. 158: 566.
https://www.ncbi.nlm.nih.gov/pubmed/9224361
569. Blumenthal, I. Vesicoureteric reflux and urinary tract infection in children. Postgrad Med J, 2006. 82: 31.
https://www.ncbi.nlm.nih.gov/pubmed/16397077
570. Darge, K., *et al.* Current status of vesicoureteral reflux diagnosis. World J Urol, 2004. 22: 88.
https://www.ncbi.nlm.nih.gov/pubmed/15173954
571. Lebowitz, R.L., *et al.* International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. Pediatr Radiol, 1985. 15: 105.
https://www.ncbi.nlm.nih.gov/pubmed/3975102
572. Westwood, M.E., *et al.* Further investigation of confirmed urinary tract infection (UTI) in children under five years: a systematic review. BMC Pediatr, 2005. 5: 2.
https://www.ncbi.nlm.nih.gov/pubmed/15769296
573. Snow, B.W., *et al.* Non-invasive vesicoureteral reflux imaging. J Pediatr Urol, 2010. 6: 543.
https://www.ncbi.nlm.nih.gov/pubmed/20488755

574. Darge, K. Voiding urosonography with US contrast agents for the diagnosis of vesicoureteric reflux in children. II. Comparison with radiological examinations. Pediatr Radiol, 2008. 38: 54. https://www.ncbi.nlm.nih.gov/pubmed/17639371
575. Papadopoulou, F., *et al.* Harmonic voiding urosonography with a second-generation contrast agent for the diagnosis of vesicoureteral reflux. Pediatr Radiol, 2009. 39: 239. https://www.ncbi.nlm.nih.gov/pubmed/19096835
576. Takazakura, R., *et al.* Magnetic resonance voiding cystourethrography for vesicoureteral reflux. J Magn Reson Imaging, 2007. 25: 170. https://www.ncbi.nlm.nih.gov/pubmed/17154372
577. Medical versus surgical treatment of primary vesicoureteral reflux: report of the International Reflux Study Committee. Pediatrics, 1981. 67: 392. https://www.ncbi.nlm.nih.gov/pubmed/7017578
578. Scherz, H.C., *et al.* The selective use of dimercaptosuccinic acid renal scans in children with vesicoureteral reflux. J Urol, 1994. 152: 628. https://www.ncbi.nlm.nih.gov/pubmed/8021985
579. Hoberman, A., *et al.* Imaging studies after a first febrile urinary tract infection in young children. N Engl J Med, 2003. 348: 195. https://www.ncbi.nlm.nih.gov/pubmed/12529459
580. Grazioli, S., *et al.* Antenatal and postnatal ultrasound in the evaluation of the risk of vesicoureteral reflux. Pediatr Nephrol, 2010. 25: 1687. https://www.ncbi.nlm.nih.gov/pubmed/20524012
581. Lidefelt, K.J., *et al.* Antenatal hydronephrosis: infants with minor postnatal dilatation do not need prophylaxis. Pediatr Nephrol, 2008. 23: 2021. https://www.ncbi.nlm.nih.gov/pubmed/18560902
582. Hafez, A.T., *et al.* Analysis of trends on serial ultrasound for high grade neonatal hydronephrosis. J Urol, 2002. 168: 1518. https://www.ncbi.nlm.nih.gov/pubmed/12352447
583. Lee, J.H., *et al.* Nonrefluxing neonatal hydronephrosis and the risk of urinary tract infection. J Urol, 2008. 179: 1524. https://www.ncbi.nlm.nih.gov/pubmed/18295269
584. Sidhu, G., *et al.* Outcome of isolated antenatal hydronephrosis: a systematic review and meta-analysis. Pediatr Nephrol, 2006. 21: 218. https://www.ncbi.nlm.nih.gov/pubmed/16362721
585. Houle, A.M., *et al.* Impact of early screening for reflux in siblings on the detection of renal damage. BJU Int, 2004. 94: 123. https://www.ncbi.nlm.nih.gov/pubmed/15217445
586. Puri, P., *et al.* Urinary tract infection and renal damage in sibling vesicoureteral reflux. J Urol, 1998. 160: 1028. https://www.ncbi.nlm.nih.gov/pubmed/9719271
587. Shaikh, N., *et al.* Identification of children and adolescents at risk for renal scarring after a first urinary tract infection: a meta-analysis with individual patient data. JAMA Pediatr, 2014. 168: 893. https://www.ncbi.nlm.nih.gov/pubmed/25089634
588. Hansson, S., *et al.* Dimercapto-succinic acid scintigraphy instead of voiding cystourethrography for infants with urinary tract infection. J Urol, 2004. 172: 1071. https://www.ncbi.nlm.nih.gov/pubmed/15311040
589. Herz, D., *et al.* 5-year prospective results of dimercapto-succinic acid imaging in children with febrile urinary tract infection: proof that the top-down approach works. J Urol, 2010. 184: 1703. https://www.ncbi.nlm.nih.gov/pubmed/20728131
590. Preda, I., *et al.* Normal dimercaptosuccinic acid scintigraphy makes voiding cystourethrography unnecessary after urinary tract infection. J Pediatr, 2007. 151: 581. https://www.ncbi.nlm.nih.gov/pubmed/18035134
591. Colen, J., *et al.* Dysfunctional elimination syndrome is a negative predictor for vesicoureteral reflux. J Pediatr Urol, 2006. 2: 312. https://www.ncbi.nlm.nih.gov/pubmed/18947628
592. Elder, J.S., *et al.* Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. J Urol, 1997. 157: 1846. https://www.ncbi.nlm.nih.gov/pubmed/9112544
593. Dias, C.S., *et al.* Risk factors for recurrent urinary tract infections in a cohort of patients with primary vesicoureteral reflux. Pediatr Infect Dis J, 2010. 29: 139. https://www.ncbi.nlm.nih.gov/pubmed/20135833

594. Wheeler, D.M., *et al.* Interventions for primary vesicoureteric reflux. Cochrane Database Syst Rev, 2004: CD001532.
https://www.ncbi.nlm.nih.gov/pubmed/15266449
595. Williams, G.J., *et al.* Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database Syst Rev, 2006: CD001534.
https://www.ncbi.nlm.nih.gov/pubmed/16855971
596. Singh-Grewal, D., *et al.* Circumcision for the prevention of urinary tract infection in boys: a systematic review of randomised trials and observational studies. Arch Dis Child, 2005. 90: 853.
https://www.ncbi.nlm.nih.gov/pubmed/15890696
597. Brandstrom, P., *et al.* The Swedish reflux trial in children: IV. Renal damage. J Urol, 2010. 184: 292.
https://www.ncbi.nlm.nih.gov/pubmed/20494369
598. Greenfield, S.P. Antibiotic prophylaxis in pediatric urology: an update. Curr Urol Rep, 2011. 12: 126.
https://www.ncbi.nlm.nih.gov/pubmed/21229337
599. Greenfield, S.P., *et al.* Vesicoureteral reflux: the RIVUR study and the way forward. J Urol, 2008. 179: 405.
https://www.ncbi.nlm.nih.gov/pubmed/18076937
600. Brandstrom, P., *et al.* The Swedish reflux trial in children: III. Urinary tract infection pattern. J Urol, 2010. 184: 286.
https://www.ncbi.nlm.nih.gov/pubmed/20488494
601. Hoberman, A., *et al.* Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med, 2014. 370: 2367.
https://www.ncbi.nlm.nih.gov/pubmed/24795142
602. Mathews, R., *et al.* The role of antimicrobial prophylaxis in the management of children with vesicoureteral reflux--the RIVUR study outcomes. Adv Chronic Kidney Dis, 2015. 22: 325.
https://www.ncbi.nlm.nih.gov/pubmed/26088078
603. Hidas, G., *et al.* Predicting the Risk of Breakthrough Urinary Tract Infections: Primary Vesicoureteral Reflux. J Urol, 2015. 194: 1396.
https://www.ncbi.nlm.nih.gov/pubmed/26066405
604. de Bessa, J., Jr., *et al.* Antibiotic prophylaxis for prevention of febrile urinary tract infections in children with vesicoureteral reflux: a meta-analysis of randomized, controlled trials comparing dilated to nondilated vesicoureteral reflux. J Urol, 2015. 193: 1772.
https://www.ncbi.nlm.nih.gov/pubmed/25817142
605. Dogan, H.S., *et al.* Factors affecting the success of endoscopic treatment of vesicoureteral reflux and comparison of two dextranomer based bulking agents: does bulking substance matter? J Pediatr Urol, 2015. 11: 90.e1.
https://www.ncbi.nlm.nih.gov/pubmed/24095906
606. Kocherov, S., *et al.* Multicenter survey of endoscopic treatment of vesicoureteral reflux using polyacrylate-polyalcohol bulking copolymer (Vantris). Urology, 2014. 84: 689.
https://www.ncbi.nlm.nih.gov/pubmed/25168553
607. Puri, P., *et al.* Multicenter survey of endoscopic treatment of vesicoureteral reflux using polytetrafluoroethylene. J Urol, 1998. 160: 1007.
https://www.ncbi.nlm.nih.gov/pubmed/9719265
608. Steyaert, H., *et al.* Migration of PTFE paste particles to the kidney after treatment for vesico-ureteric reflux. BJU Int, 2000. 85: 168.
https://www.ncbi.nlm.nih.gov/pubmed/10619969
609. Lightner, D.J. Review of the available urethral bulking agents. Curr Opin Urol, 2002. 12: 333.
https://www.ncbi.nlm.nih.gov/pubmed/12072655
610. Elder, J.S., *et al.* Endoscopic therapy for vesicoureteral reflux: a meta-analysis. I. Reflux resolution and urinary tract infection. J Urol, 2006. 175: 716.
https://www.ncbi.nlm.nih.gov/pubmed/16407037
611. Holmdahl, G., *et al.* The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. J Urol, 2010. 184: 280.
https://www.ncbi.nlm.nih.gov/pubmed/20488469
612. Duckett, J.W., *et al.* Surgical results: International Reflux Study in Children--United States branch. J Urol, 1992. 148: 1674.
https://www.ncbi.nlm.nih.gov/pubmed/9507881
613. Lipski, B.A., *et al.* Voiding dysfunction after bilateral extravesical ureteral reimplantation. J Urol, 1998. 159: 1019.
https://www.ncbi.nlm.nih.gov/pubmed/9474222

614. Marchini, G.S., *et al.* Robotic assisted laparoscopic ureteral reimplantation in children: case matched comparative study with open surgical approach. J Urol, 2011. 185: 1870. https://www.ncbi.nlm.nih.gov/pubmed/9474222
615. Kasturi, S., *et al.* Prospective long-term analysis of nerve-sparing extravesical robotic-assisted laparoscopic ureteral reimplantation. Urology, 2012. 79: 680. https://www.ncbi.nlm.nih.gov/pubmed/22197530
616. Austin, J.C., *et al.* Vesicoureteral reflux: who benefits from correction. Urol Clin North Am, 2010. 37: 243. https://www.ncbi.nlm.nih.gov/pubmed/20569802
617. Canon, S.J., *et al.* Vesicoscopic cross-trigonal ureteral reimplantation: a minimally invasive option for repair of vesicoureteral reflux. J Urol, 2007. 178: 269. https://www.ncbi.nlm.nih.gov/pubmed/17499791
618. Chung, P.H., *et al.* Comparing open and pneumovesical approach for ureteric reimplantation in pediatric patients--a preliminary review. J Pediatr Surg, 2008. 43: 2246. https://www.ncbi.nlm.nih.gov/pubmed/19040945
619. El-Ghoneimi, A. Paediatric laparoscopic surgery. Curr Opin Urol, 2003. 13: 329. https://www.ncbi.nlm.nih.gov/pubmed/12811298
620. Janetschek, G., *et al.* Laparoscopic ureteral anti-reflux plasty reimplantation. First clinical experience. Ann Urol (Paris), 1995. 29: 101. https://www.ncbi.nlm.nih.gov/pubmed/7645993
621. Jayanthi, V., *et al.* Vesicoscopic ureteral reimplantation: a minimally invasive technique for the definitive repair of vesicoureteral reflux. Adv Urol, 2008: 973616. https://www.ncbi.nlm.nih.gov/pubmed/17499791
622. Riquelme, M., *et al.* Laparoscopic extravesical transperitoneal approach for vesicoureteral reflux. J Laparoendosc Adv Surg Tech A, 2006. 16: 312. https://www.ncbi.nlm.nih.gov/pubmed/16796449
623. Grimsby, G.M., *et al.* Multi-institutional review of outcomes of robot-assisted laparoscopic extravesical ureteral reimplantation. J Urol, 2015. 193: 1791. https://www.ncbi.nlm.nih.gov/pubmed/25301094
624. Straub, M., *et al.* Diagnosis and metaphylaxis of stone disease. Consensus concept of the National Working Committee on Stone Disease for the upcoming German Urolithiasis Guideline. World J Urol, 2005. 23: 309. https://www.ncbi.nlm.nih.gov/pubmed/16315051
625. Metcalfe, P.D., *et al.* What is the need for additional bladder surgery after bladder augmentation in childhood? J Urol, 2006. 176: 1801. https://www.ncbi.nlm.nih.gov/pubmed/16945653
626. Bush, N.C., *et al.* Hospitalizations for pediatric stone disease in United States, 2002-2007. J Urol, 2010. 183: 1151. https://www.ncbi.nlm.nih.gov/pubmed/20096871
627. Novak, T.E., *et al.* Sex prevalence of pediatric kidney stone disease in the United States: an epidemiologic investigation. Urology, 2009. 74: 104. https://www.ncbi.nlm.nih.gov/pubmed/19428065
628. Tasian, G.E., *et al.* Annual Incidence of Nephrolithiasis among Children and Adults in South Carolina from 1997 to 2012. Clin J Am Soc Nephrol, 2016. 11: 488. https://www.ncbi.nlm.nih.gov/pubmed/26769765
629. Sas, D.J., *et al.* Increasing incidence of kidney stones in children evaluated in the emergency department. J Pediatr, 2010. 157: 132. https://www.ncbi.nlm.nih.gov/pubmed/20362300
630. Kirejczyk, J.K., *et al.* An association between kidney stone composition and urinary metabolic disturbances in children. J Pediatr Urol, 2014. 10: 130. https://www.ncbi.nlm.nih.gov/pubmed/23953243
631. Kruse, K., *et al.* Reference values for urinary calcium excretion and screening for hypercalciuria in children and adolescents. Eur J Pediatr, 1984. 143: 25. https://www.ncbi.nlm.nih.gov/pubmed/6510426
632. Sargent, J.D., *et al.* Normal values for random urinary calcium to creatinine ratios in infancy. J Pediatr, 1993. 123: 393. https://www.ncbi.nlm.nih.gov/pubmed/8355114
633. Stapleton, F.B., *et al.* Urinary excretion of calcium following an oral calcium loading test in healthy children. Pediatrics, 1982. 69: 594. https://www.ncbi.nlm.nih.gov/pubmed/7079015

634. Stapleton, F.B., *et al.* Hypercalciuria in children with urolithiasis. Am J Dis Child, 1982. 136: 675. https://www.ncbi.nlm.nih.gov/pubmed/7102617
635. Borghi, L., *et al.* Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med, 2002. 346: 77. https://www.ncbi.nlm.nih.gov/pubmed/
636. Curhan, G.C., *et al.* A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med, 1993. 328: 833. https://www.ncbi.nlm.nih.gov/pubmed/8441427
637. Bartosh, S.M. Medical management of pediatric stone disease. Urol Clin North Am, 2004. 31: 575. https://www.ncbi.nlm.nih.gov/pubmed/15313066
638. Preminger, G.M., *et al.* Eventual attenuation of hypocalciuric response to hydrochlorothiazide in absorptive hypercalciuria. J Urol, 1987. 137: 1104. https://www.ncbi.nlm.nih.gov/pubmed/3586136
639. Choi, J.N., *et al.* Low-dose thiazide diuretics in children with idiopathic renal hypercalciuria. Acta Paediatr, 2011. 100: e71. https://www.ncbi.nlm.nih.gov/pubmed/21284722
640. Naseri, M., *et al.* Role of high-dose hydrochlorothiazide in idiopathic hypercalciuric urolithiasis of childhood. Iran J Kidney Dis, 2011. 5: 162. https://www.ncbi.nlm.nih.gov/pubmed/21525575
641. Tekin, A., *et al.* Oral potassium citrate treatment for idiopathic hypocitruria in children with calcium urolithiasis. J Urol, 2002. 168: 2572. https://www.ncbi.nlm.nih.gov/pubmed/12441986
642. Neuhaus, T.J., *et al.* Urinary oxalate excretion in urolithiasis and nephrocalcinosis. Arch Dis Child, 2000. 82: 322. https://www.ncbi.nlm.nih.gov/pubmed/10735843
643. Hoppe, B., *et al.* Urinary calcium oxalate saturation in healthy infants and children. J Urol, 1997. 158: 557. https://www.ncbi.nlm.nih.gov/pubmed/9224359
644. Turudic, D., *et al.* Calcium oxalate urolithiasis in children: urinary promoters/inhibitors and role of their ratios. Eur J Pediatr, 2016. 175: 1959. https://www.ncbi.nlm.nih.gov/pubmed/27730307
645. Morgenstern, B.Z., *et al.* Urinary oxalate and glycolate excretion patterns in the first year of life: a longitudinal study. J Pediatr, 1993. 123: 248. https://www.ncbi.nlm.nih.gov/pubmed/8345420
646. Defoor, W., *et al.* Results of a prospective trial to compare normal urine supersaturation in children and adults. J Urol, 2005. 174: 1708. https://www.ncbi.nlm.nih.gov/pubmed/16148687
647. Tekin, A., *et al.* A study of the etiology of idiopathic calcium urolithiasis in children: hypocitruria is the most important risk factor. J Urol, 2000. 164: 162. https://www.ncbi.nlm.nih.gov/pubmed/10840454
648. Kovacevic, L., *et al.* From hypercalciuria to hypocitraturia--a shifting trend in pediatric urolithiasis? J Urol, 2012. 188: 1623. https://www.ncbi.nlm.nih.gov/pubmed/22910255
649. Celiksoy, M.H., *et al.* Metabolic disorders in Turkish children with urolithiasis. Urology, 2015. 85: 909. https://www.ncbi.nlm.nih.gov/pubmed/25817115
650. Tekin, A., *et al.* Cystine calculi in children: the results of a metabolic evaluation and response to medical therapy. J Urol, 2001. 165: 2328. https://www.ncbi.nlm.nih.gov/pubmed/11371943
651. Gabrielsen, J.S., *et al.* Pediatric urinary stone composition in the United States. J Urol, 2012. 187: 2182. https://www.ncbi.nlm.nih.gov/pubmed/22503021
652. Rellum, D.M., *et al.* Pediatric urolithiasis in a non-endemic country: a single center experience from The Netherlands. J Pediatr Urol, 2014. 10: 155. https://www.ncbi.nlm.nih.gov/pubmed/23981680
653. Bove, P., *et al.* Reexamining the value of hematuria testing in patients with acute flank pain. J Urol, 1999. 162: 685. https://www.ncbi.nlm.nih.gov/pubmed/10458342
654. Sternberg, K., *et al.* Pediatric stone disease: an evolving experience. J Urol, 2005. 174: 1711. https://www.ncbi.nlm.nih.gov/pubmed/16148688

655. Oner, S., *et al.* Comparison of spiral CT and US in the evaluation of pediatric urolithiasis. Jbr-btr, 2004. 87: 219.
https://www.ncbi.nlm.nih.gov/pubmed/15587558
656. Memarsadeghi, M., *et al.* Unenhanced multi-detector row CT in patients suspected of having urinary stone disease: effect of section width on diagnosis. Radiology, 2005. 235: 530.
https://www.ncbi.nlm.nih.gov/pubmed/15758192
657. Strouse, P.J., *et al.* Non-contrast thin-section helical CT of urinary tract calculi in children. Pediatr Radiol, 2002. 32: 326.
https://www.ncbi.nlm.nih.gov/pubmed/11956719
658. Kwon, J.K., *et al.* Usefulness of low-dose nonenhanced computed tomography with iterative reconstruction for evaluation of urolithiasis: diagnostic performance and agreement between the urologist and the radiologist. Urology, 2015. 85: 531.
https://www.ncbi.nlm.nih.gov/pubmed/25733262
659. Skolarikos, A., *et al.* Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines. Eur Urol, 2015. 67: 750.
https://www.ncbi.nlm.nih.gov/pubmed/25454613
660. Tekin, A., *et al.* Ureteropelvic junction obstruction and coexisting renal calculi in children: role of metabolic abnormalities. Urology, 2001. 57: 542.
https://www.ncbi.nlm.nih.gov/pubmed/11248635
661. Alpay, H., *et al.* Clinical and metabolic features of urolithiasis and microlithiasis in children. Pediatr Nephrol, 2009. 24: 2203.
https://www.ncbi.nlm.nih.gov/pubmed/19603196
662. Raza, A., *et al.* Pediatric urolithiasis: 15 years of local experience with minimally invasive endourological management of pediatric calculi. J Urol, 2005. 174: 682.
https://www.ncbi.nlm.nih.gov/pubmed/16006948
663. Rizvi, S.A., *et al.* Pediatric urolithiasis: developing nation perspectives. J Urol, 2002. 168: 1522.
https://www.ncbi.nlm.nih.gov/pubmed/12352448
664. Shahat, A., *et al.* Is Tamsulosin Effective after Shock Wave Lithotripsy for Pediatric Renal Stones? A Randomized, Controlled Study. J Urol, 2016. 195: 1284.
https://www.ncbi.nlm.nih.gov/pubmed/26926538
665. Velazquez, N., *et al.* Medical expulsive therapy for pediatric urolithiasis: Systematic review and meta-analysis. J Pediatr Urol, 2015. 11: 321.
https://www.ncbi.nlm.nih.gov/pubmed/26165192
666. Dincel, N., *et al.* Are small residual stone fragments really insignificant in children? J Pediatr Surg, 2013. 48: 840.
https://www.ncbi.nlm.nih.gov/pubmed/23583144
667. El-Assmy, A., *et al.* Clinically Insignificant Residual Fragments: Is It an Appropriate Term in Children? Urology, 2015. 86: 593.
https://www.ncbi.nlm.nih.gov/pubmed/26126693
668. Reisiger, K., *et al.* Pediatric nephrolithiasis: does treatment affect renal growth? Urology, 2007. 69: 1190.
https://www.ncbi.nlm.nih.gov/pubmed/17572213
669. Akin, Y., *et al.* Long-term effects of pediatric extracorporeal shockwave lithotripsy on renal function. Res Rep Urol, 2014. 6: 21.
https://www.ncbi.nlm.nih.gov/pubmed/24892029
670. Willis, L.R., *et al.* Relationship between kidney size, renal injury, and renal impairment induced by shock wave lithotripsy. J Am Soc Nephrol, 1999. 10: 1753.
https://www.ncbi.nlm.nih.gov/pubmed/10446943
671. Villanyi, K.K., *et al.* Short-term changes in renal function after extracorporeal shock wave lithotripsy in children. J Urol, 2001. 166: 222.
https://www.ncbi.nlm.nih.gov/pubmed/11435873
672. Aldridge, R.D., *et al.* Anesthesia for pediatric lithotripsy. Paediatr Anaesth, 2006. 16: 236.
https://www.ncbi.nlm.nih.gov/pubmed/16490086
673. McLorie, G.A., *et al.* Safety and efficacy of extracorporeal shock wave lithotripsy in infants. Can J Urol, 2003. 10: 2051.
https://www.ncbi.nlm.nih.gov/pubmed/14704109
674. Aksoy, Y., *et al.* Extracorporeal shock wave lithotripsy in children: experience using a mpl-9000 lithotriptor. World J Urol, 2004. 22: 115.
https://www.ncbi.nlm.nih.gov/pubmed/14740160

675. Vlajkovic, M., *et al.* Long-term functional outcome of kidneys in children with urolithiasis after ESWL treatment. Eur J Pediatr Surg, 2002. 12: 118.
https://www.ncbi.nlm.nih.gov/pubmed/12015657
676. Muslumanoglu, A.Y., *et al.* Extracorporeal shock wave lithotripsy as first line treatment alternative for urinary tract stones in children: a large scale retrospective analysis. J Urol, 2003. 170: 2405.
https://www.ncbi.nlm.nih.gov/pubmed/14634438
677. Ather, M.H., *et al.* Does size and site matter for renal stones up to 30-mm in size in children treated by extracorporeal lithotripsy? Urology, 2003. 61: 212.
https://www.ncbi.nlm.nih.gov/pubmed/12559298
678. Ugur, G., *et al.* Anaesthetic/analgesic management of extracorporeal shock wave lithotripsy in paediatric patients. Paediatr Anaesth, 2003. 13: 85.
https://www.ncbi.nlm.nih.gov/pubmed/12535048
679. Rodrigues Netto, N., Jr., *et al.* Extracorporeal shock wave lithotripsy in children. J Urol, 2002. 167: 2164.
https://www.ncbi.nlm.nih.gov/pubmed/11956471
680. Afshar, K., *et al.* Outcome of small residual stone fragments following shock wave lithotripsy in children. J Urol, 2004. 172: 1600.
https://www.ncbi.nlm.nih.gov/pubmed/15371769
681. Tan, A.H., *et al.* Results of shockwave lithotripsy for pediatric urolithiasis. J Endourol, 2004. 18: 527.
https://www.ncbi.nlm.nih.gov/pubmed/15333214
682. Lottmann, H.B., *et al.* Monotherapy extracorporeal shock wave lithotripsy for the treatment of staghorn calculi in children. J Urol, 2001. 165: 2324.
https://www.ncbi.nlm.nih.gov/pubmed/11371942
683. Al-Busaidy, S.S., *et al.* Pediatric staghorn calculi: the role of extracorporeal shock wave lithotripsy monotherapy with special reference to ureteral stenting. J Urol, 2003. 169: 629.
https://www.ncbi.nlm.nih.gov/pubmed/12544330
684. Ozgur Tan, M., *et al.* Extracorporeal shock-wave lithotripsy for treatment of ureteral calculi in paediatric patients. Pediatr Surg Int, 2003. 19: 471.
https://www.ncbi.nlm.nih.gov/pubmed/12736749
685. Onal, B., *et al.* The impact of caliceal pelvic anatomy on stone clearance after shock wave lithotripsy for pediatric lower pole stones. J Urol, 2004. 172: 1082.
https://www.ncbi.nlm.nih.gov/pubmed/15311043
686. Ozgur Tan, M., *et al.* The impact of radiological anatomy in clearance of lower calyceal stones after shock wave lithotripsy in paediatric patients. Eur Urol, 2003. 43: 188.
https://www.ncbi.nlm.nih.gov/pubmed/12565778
687. Demirkesen, O., *et al.* Efficacy of extracorporeal shock wave lithotripsy for isolated lower caliceal stones in children compared with stones in other renal locations. Urology, 2006. 67: 170.
https://www.ncbi.nlm.nih.gov/pubmed/16413356
688. Hochreiter, W.W., *et al.* Extracorporeal shock wave lithotripsy for distal ureteral calculi: what a powerful machine can achieve. J Urol, 2003. 169: 878.
https://www.ncbi.nlm.nih.gov/pubmed/12576804
689. Landau, E.H., *et al.* Extracorporeal shock wave lithotripsy is highly effective for ureteral calculi in children. J Urol, 2001. 165: 2316.
https://www.ncbi.nlm.nih.gov/pubmed/11371970
690. McAdams, S., *et al.* Preoperative Stone Attenuation Value Predicts Success After Shock Wave Lithotripsy in Children. J Urol, 2010. 184: 1804.
http://www.sciencedirect.com/science/article/pii/S0022534710032106
691. Onal, B., *et al.* Nomogram and scoring system for predicting stone-free status after extracorporeal shock wave lithotripsy in children with urolithiasis. BJU Int, 2013. 111: 344.
https://www.ncbi.nlm.nih.gov/pubmed/22672514
692. Dogan, H.S., *et al.* A new nomogram for prediction of outcome of pediatric shock-wave lithotripsy. J Pediatr Urol, 2015. 11: 84 e1.
https://www.ncbi.nlm.nih.gov/pubmed/25812469
693. Wu, H.Y., *et al.* Surgical management of children with urolithiasis. Urol Clin North Am, 2004. 31: 589.
https://www.ncbi.nlm.nih.gov/pubmed/15313067
694. Desai, M.R., *et al.* Percutaneous nephrolithotomy for complex pediatric renal calculus disease. J Endourol, 2004. 18: 23.
https://www.ncbi.nlm.nih.gov/pubmed/15006048

695. Soygur, T., *et al.* Hydrodilation of the ureteral orifice in children renders ureteroscopic access possible without any further active dilation. J Urol, 2006. 176: 285.
https://www.ncbi.nlm.nih.gov/pubmed/16753421
696. Caione, P., *et al.* Endoscopic manipulation of ureteral calculi in children by rigid operative ureterorenoscopy. J Urol, 1990. 144: 484.
https://www.ncbi.nlm.nih.gov/pubmed/2374225
697. Thomas, J.C., *et al.* Pediatric ureteroscopic stone management. J Urol, 2005. 174: 1072.
https://www.ncbi.nlm.nih.gov/pubmed/18804225
698. Dogan, H.S., *et al.* Use of the holmium:YAG laser for ureterolithotripsy in children. BJU Int, 2004. 94: 131.
https://www.ncbi.nlm.nih.gov/pubmed/15217447
699. De Dominicis, M., *et al.* Retrograde ureteroscopy for distal ureteric stone removal in children. BJU Int, 2005. 95: 1049.
https://www.ncbi.nlm.nih.gov/pubmed/15839930
700. Satar, N., *et al.* Rigid ureteroscopy for the treatment of ureteral calculi in children. J Urol, 2004. 172: 298.
https://www.ncbi.nlm.nih.gov/pubmed/15201799
701. Raza, A., *et al.* Ureteroscopy in the management of pediatric urinary tract calculi. J Endourol, 2005. 19: 151.
https://www.ncbi.nlm.nih.gov/pubmed/15798409
702. Bassiri, A., *et al.* Transureteral lithotripsy in pediatric practice. J Endourol, 2002. 16: 257.
https://www.ncbi.nlm.nih.gov/pubmed/12042111
703. Van Savage, J.G., *et al.* Treatment of distal ureteral stones in children: similarities to the american urological association guidelines in adults. J Urol, 2000. 164: 1089.
https://www.ncbi.nlm.nih.gov/pubmed/10958749
704. Jackman, S.V., *et al.* Percutaneous nephrolithotomy in infants and preschool age children: experience with a new technique. Urology, 1998. 52: 697.
https://www.ncbi.nlm.nih.gov/pubmed/9763096
705. ElSheemy, M.S., *et al.* Lower calyceal and renal pelvic stones in preschool children: A comparative study of mini-percutaneous nephrolithotomy versus extracorporeal shockwave lithotripsy. Int J Urol, 2016. 23: 564.
https://www.ncbi.nlm.nih.gov/pubmed/27173126
706. Badawy, H., *et al.* Percutaneous management of renal calculi: experience with percutaneous nephrolithotomy in 60 children. J Urol, 1999. 162: 1710.
https://www.ncbi.nlm.nih.gov/pubmed/10524919
707. Dawaba, M.S., *et al.* Percutaneous nephrolithotomy in children: early and late anatomical and functional results. J Urol, 2004. 172: 1078.
https://www.ncbi.nlm.nih.gov/pubmed/15311042
708. Boormans, J.L., *et al.* Percutaneous nephrolithotomy for treating renal calculi in children. BJU Int, 2005. 95: 631.
https://www.ncbi.nlm.nih.gov/pubmed/15705093
709. Shokeir, A.A., *et al.* Percutaneous nephrolithotomy in treatment of large stones within horseshoe kidneys. Urology, 2004. 64: 426.
https://www.ncbi.nlm.nih.gov/pubmed/15311042
710. Sahin, A., *et al.* Percutaneous nephrolithotomy in older children. J Pediatr Surg, 2000. 35: 1336.
https://www.ncbi.nlm.nih.gov/pubmed/10999692
711. Ozden, E., *et al.* Modified Clavien classification in percutaneous nephrolithotomy: assessment of complications in children. J Urol, 2011. 185: 264.
https://www.ncbi.nlm.nih.gov/pubmed/21074805
712. Guven, S., *et al.* Successful percutaneous nephrolithotomy in children: multicenter study on current status of its use, efficacy and complications using Clavien classification. J Urol, 2011. 185: 1419.
https://www.ncbi.nlm.nih.gov/pubmed/21334653
713. Dogan, H.S., *et al.* Percutaneous nephrolithotomy in children: does age matter? World J Urol, 2011. 29: 725.
https://www.ncbi.nlm.nih.gov/pubmed/21590468
714. Khairy Salem, H., *et al.* Tubeless percutaneous nephrolithotomy in children. J Pediatr Urol, 2007. 3: 235.
https://www.ncbi.nlm.nih.gov/pubmed/18947742

715. Unsal, A., *et al.* Safety and efficacy of percutaneous nephrolithotomy in infants, preschool age, and older children with different sizes of instruments. Urology, 2010. 76: 247.
https://www.ncbi.nlm.nih.gov/pubmed/20022089
716. Nouralizadeh, A., *et al.* Experience of percutaneous nephrolithotomy using adult-size instruments in children less than 5 years old. J Pediatr Urol, 2009. 5: 351.
https://www.ncbi.nlm.nih.gov/pubmed/19230776
717. Ozden, E., *et al.* Percutaneous renal surgery in children with complex stones. J Pediatr Urol, 2008. 4: 295.
https://www.ncbi.nlm.nih.gov/pubmed/18644533
718. Onal, B., *et al.* Factors affecting complication rates of percutaneous nephrolithotomy in children: results of a multi-institutional retrospective analysis by the Turkish pediatric urology society. J Urol, 2014. 191: 777.
https://www.ncbi.nlm.nih.gov/pubmed/24095906
719. Bilen, C.Y., *et al.* Tubeless mini percutaneous nephrolithotomy in infants and preschool children: a preliminary report. J Urol, 2010. 184: 2498.
https://www.ncbi.nlm.nih.gov/pubmed/20961572
720. Bilen, C.Y., *et al.* Percutaneous nephrolithotomy in children: lessons learned in 5 years at a single institution. J Urol, 2007. 177: 1867.
https://www.ncbi.nlm.nih.gov/pubmed/17437838
721. Jackman, S.V., *et al.* The “mini-perc” technique: a less invasive alternative to percutaneous nephrolithotomy. World J Urol, 1998. 16: 371.
https://www.ncbi.nlm.nih.gov/pubmed/9870281
722. Dede, O., *et al.* Ultra-mini-percutaneous nephrolithotomy in pediatric nephrolithiasis: Both low pressure and high efficiency. J Pediatr Urol, 2015. 11: 253 e1.
https://www.ncbi.nlm.nih.gov/pubmed/25964199
723. Desai, M.R., *et al.* Single-step percutaneous nephrolithotomy (microperc): the initial clinical report. J Urol, 2011. 186: 140.
https://www.ncbi.nlm.nih.gov/pubmed/21575966
724. Hatipoglu, N.K., *et al.* Comparison of shockwave lithotripsy and microperc for treatment of kidney stones in children. J Endourol, 2013. 27: 1141.
https://www.ncbi.nlm.nih.gov/pubmed/23713511
725. Karatag, T., *et al.* A Comparison of 2 Percutaneous Nephrolithotomy Techniques for the Treatment of Pediatric Kidney Stones of Sizes 10-20 mm: Microperc vs Miniperc. Urology, 2015. 85: 1015.
https://www.ncbi.nlm.nih.gov/pubmed/25917724
726. Aghamir, S.M., *et al.* Feasibility of totally tubeless percutaneous nephrolithotomy under the age of 14 years: a randomized clinical trial. J Endourol, 2012. 26: 621.
https://www.ncbi.nlm.nih.gov/pubmed/22192104
727. Bodakci, M.N., *et al.* Ultrasound-guided micropercutaneous nephrolithotomy in pediatric patients with kidney stones. Int J Urol, 2015. 22: 773.
https://www.ncbi.nlm.nih.gov/pubmed/25975519
728. Gamal, W., *et al.* Supine pediatric percutaneous nephrolithotomy (PCNL). J Pediatr Urol, 2015. 11: 78 e1.
https://www.ncbi.nlm.nih.gov/pubmed/25819602
729. Richter, S., *et al.* Early postureteroscopy vesicoureteral reflux--a temporary and infrequent complication: prospective study. J Endourol, 1999. 13: 365.
https://www.ncbi.nlm.nih.gov/pubmed/10446797
730. Schuster, T.G., *et al.* Ureteroscopy for the treatment of urolithiasis in children. J Urol, 2002. 167: 1813.
https://www.ncbi.nlm.nih.gov/pubmed/11912438
731. al Busaidy, S.S., *et al.* Paediatric ureteroscopy for ureteric calculi: a 4-year experience. Br J Urol, 1997. 80: 797.
https://www.ncbi.nlm.nih.gov/pubmed/9393306
732. Hill, D.E., *et al.* Ureteroscopy in children. J Urol, 1990. 144: 481.
https://www.ncbi.nlm.nih.gov/pubmed/2374224
733. Gokce, M.I., *et al.* Evaluation of Postoperative Hydronephrosis Following Ureteroscopy in Pediatric Population: Incidence and Predictors. Urology, 2016. 93: 164.
https://www.ncbi.nlm.nih.gov/pubmed/26972147

734. Dogan, H.S., *et al.* Factors affecting complication rates of ureteroscopic lithotripsy in children: results of multi-institutional retrospective analysis by Pediatric Stone Disease Study Group of Turkish Pediatric Urology Society. J Urol, 2011. 186: 1035.
https://www.ncbi.nlm.nih.gov/pubmed/24095906
735. Abu Ghazaleh, L.A., *et al.* Retrograde intrarenal lithotripsy for small renal stones in prepubertal children. Saudi J Kidney Dis Transpl, 2011. 22: 492.
https://www.ncbi.nlm.nih.gov/pubmed/21566306
736. Corcoran, A.T., *et al.* When is prior ureteral stent placement necessary to access the upper urinary tract in prepubertal children? J Urol, 2008. 180: 1861.
https://www.ncbi.nlm.nih.gov/pubmed/18721946
737. Kim, S.S., *et al.* Pediatric flexible ureteroscopic lithotripsy: the children's hospital of Philadelphia experience. J Urol, 2008. 180: 2616.
https://www.ncbi.nlm.nih.gov/pubmed/18950810
738. Dave, S., *et al.* Single-institutional study on role of ureteroscopy and retrograde intrarenal surgery in treatment of pediatric renal calculi. Urology, 2008. 72: 1018.
https://www.ncbi.nlm.nih.gov/pubmed/18585764
739. Tanaka, S.T., *et al.* Pediatric ureteroscopic management of intrarenal calculi. J Urol, 2008. 180: 2150.
https://www.ncbi.nlm.nih.gov/pubmed/18804225
740. Erkurt, B., *et al.* Treatment of renal stones with flexible ureteroscopy in preschool age children. Urolithiasis, 2014. 42: 241.
https://www.ncbi.nlm.nih.gov/pubmed/24374900
741. Mokhless, I.A., *et al.* Retrograde intrarenal surgery monotherapy versus shock wave lithotripsy for stones 10 to 20 mm in preschool children: a prospective, randomized study. J Urol, 2014. 191: 1496.
https://www.ncbi.nlm.nih.gov/pubmed/24679882
742. Saad, K.S., *et al.* Percutaneous Nephrolithotomy vs Retrograde Intrarenal Surgery for Large Renal Stones in Pediatric Patients: A Randomized Controlled Trial. J Urol, 2015. 194: 1716.
https://www.ncbi.nlm.nih.gov/pubmed/26165587
743. Bas, O., *et al.* Comparison of Retrograde Intrarenal Surgery and Micro-Percutaneous Nephrolithotomy in Moderately Sized Pediatric Kidney Stones. J Endourol, 2016. 30: 765.
https://www.ncbi.nlm.nih.gov/pubmed/26983791
744. Lee, R.S., *et al.* Early results of robot assisted laparoscopic lithotomy in adolescents. J Urol, 2007. 177: 2306.
https://www.ncbi.nlm.nih.gov/pubmed/17509345
745. Casale, P., *et al.* Transperitoneal laparoscopic pyelolithotomy after failed percutaneous access in the pediatric patient. J Urol, 2004. 172: 680.
https://www.ncbi.nlm.nih.gov/pubmed/15247760
746. Ghani, K.R., *et al.* Robotic nephrolithotomy and pyelolithotomy with utilization of the robotic ultrasound probe. Int Braz J Urol, 2014. 40: 125.
https://www.ncbi.nlm.nih.gov/pubmed/24642160
747. Srivastava, A., *et al.* Laparoscopic Ureterolithotomy in Children: With and Without Stent - Initial Tertiary Care Center Experience with More Than 1-Year Follow-Up. Eur J Pediatr Surg, 2016.
https://www.ncbi.nlm.nih.gov/pubmed/26878339
748. Uson, A.C., *et al.* Ureteroceles in infants and children: a report based on 44 cases. Pediatrics, 1961. 27: 971.
https://www.ncbi.nlm.nih.gov/pubmed/13779382
749. Prewitt, L.H., Jr., *et al.* The single ectopic ureter. AJR Am J Roentgenol, 1976. 127: 941.
https://www.ncbi.nlm.nih.gov/pubmed/998831
750. Ahmed, S., *et al.* Single-system ectopic ureters: a review of 12 cases. J Pediatr Surg, 1992. 27: 491.
https://www.ncbi.nlm.nih.gov/pubmed/1522464
751. Chwalla, R. The process of formation of cystic dilatation of the vesical end of the ureter and of diverticula at the ureteral ostium. Urol Cutan Ren 1927. 31: 499. [No abstract available}.
752. Tokunaka, S., *et al.* Muscle dysplasia in megaureters. J Urol, 1984. 131: 383.
https://www.ncbi.nlm.nih.gov/pubmed/6699978
753. Stephens, D. Caecoureterocele and concepts on the embryology and aetiology of ureteroceles. Aust N Z J Surg, 1971. 40: 239.
https://www.ncbi.nlm.nih.gov/pubmed/5279434
754. Zerin, J.M., *et al.* Single-system ureteroceles in infants and children: imaging features. Pediatr Radiol, 2000. 30: 139.
https://www.ncbi.nlm.nih.gov/pubmed/10755749

755. Sen, S., *et al.* Single system ureteroceles in childhood. Aust N Z J Surg, 1988. 58: 903. https://www.ncbi.nlm.nih.gov/pubmed/3074770
756. Monfort, G., *et al.* Surgical management of duplex ureteroceles. J Pediatr Surg, 1992. 27: 634. https://www.ncbi.nlm.nih.gov/pubmed/1625138
757. Bolduc, S., *et al.* Histology of upper pole is unaffected by prenatal diagnosis in duplex system ureteroceles. J Urol, 2002. 168: 1123. https://www.ncbi.nlm.nih.gov/pubmed/12187250
758. Upadhyay, J., *et al.* Impact of prenatal diagnosis on the morbidity associated with ureterocele management. J Urol, 2002. 167: 2560. https://www.ncbi.nlm.nih.gov/pubmed/11992089
759. Ellerker, A.G. The extravesical ectopic ureter. Br J Surg, 1958. 45: 344. https://www.ncbi.nlm.nih.gov/pubmed/13536326
760. Di Benedetto, V., *et al.* How prenatal ultrasound can change the treatment of ectopic ureterocele in neonates? Eur J Pediatr Surg, 1997. 7: 338. https://www.ncbi.nlm.nih.gov/pubmed/9493984
761. Pfister, C., *et al.* The value of endoscopic treatment for ureteroceles during the neonatal period. J Urol, 1998. 159: 1006. https://www.ncbi.nlm.nih.gov/pubmed/9474217
762. Bozorgi, F., *et al.* Hypoplastic dysplastic kidney with a vaginal ectopic ureter identified by technetium-99m-DMSA scintigraphy. J Nucl Med, 1998. 39: 113. https://www.ncbi.nlm.nih.gov/pubmed/9443748
763. Connolly, L.P., *et al.* Ectopic ureteroceles in infants with prenatal hydronephrosis: use of renal cortical scintigraphy. Clin Nucl Med, 2002. 27: 169. https://www.ncbi.nlm.nih.gov/pubmed/11852302
764. Pattaras, J.G., *et al.* The role of 99mtechnetium dimercapto-succinic acid renal scans in the evaluation of occult ectopic ureters in girls with paradoxical incontinence. J Urol, 1999. 162: 821. https://www.ncbi.nlm.nih.gov/pubmed/10458388
765. Meneghesso, D., *et al.* Clinico-pathological correlation in duplex system ectopic ureters and ureteroceles: can preoperative work-up predict renal histology? Pediatr Surg Int, 2012. 28: 309. https://www.ncbi.nlm.nih.gov/pubmed/22127487
766. Bellah, R.D., *et al.* Ureterocele eversion with vesicoureteral reflux in duplex kidneys: findings at voiding cystourethrography. AJR Am J Roentgenol, 1995. 165: 409. https://www.ncbi.nlm.nih.gov/pubmed/7618568
767. Carrico, C., *et al.* Incontinence due to an infrasphincteric ectopic ureter: why the delay in diagnosis and what the radiologist can do about it. Pediatr Radiol, 1998. 28: 942. https://www.ncbi.nlm.nih.gov/pubmed/9880638
768. Ehammer, T., *et al.* High resolution MR for evaluation of lower urogenital tract malformations in infants and children: feasibility and preliminary experiences. Eur J Radiol, 2011. 78: 388. https://www.ncbi.nlm.nih.gov/pubmed/20138451
769. Diard, F., *et al.* [Pseudo-ureteroceles resulting from the impression of a loop of a megaureter with an ectopic subvesical orifice]. J Radiol, 1987. 68: 177. https://www.ncbi.nlm.nih.gov/pubmed/3298636
770. Sumfest, J.M., *et al.* Pseudoureterocele: potential for misdiagnosis of an ectopic ureter as a ureterocele. Br J Urol, 1995. 75: 401. https://www.ncbi.nlm.nih.gov/pubmed/7735809
771. Figueroa, V.H., *et al.* Utility of MR urography in children suspected of having ectopic ureter. Pediatr Radiol, 2014. 44: 956. https://www.ncbi.nlm.nih.gov/pubmed/24535117
772. Beganovic, A., *et al.* Ectopic ureterocele: long-term results of open surgical therapy in 54 patients. J Urol, 2007. 178: 251. https://www.ncbi.nlm.nih.gov/pubmed/17499769
773. Byun, E., *et al.* A meta-analysis of surgical practice patterns in the endoscopic management of ureteroceles. J Urol, 2006. 176: 1871. https://www.ncbi.nlm.nih.gov/pubmed/16945677
774. Chertin, B., *et al.* Endoscopic treatment of vesicoureteral reflux associated with ureterocele. J Urol, 2007. 178: 1594. https://www.ncbi.nlm.nih.gov/pubmed/17707044
775. Decter, R.M., *et al.* Individualized treatment of ureteroceles. J Urol, 1989. 142: 535. https://www.ncbi.nlm.nih.gov/pubmed/2746775

776. Husmann, D., *et al.* Management of ectopic ureterocele associated with renal duplication: a comparison of partial nephrectomy and endoscopic decompression. J Urol, 1999. 162: 1406. https://www.ncbi.nlm.nih.gov/pubmed/10492225
777. Moscovici, J., *et al.* [Management of ureteroceles with pyelo-ureteral duplication in children. Report of 64 cases]. Ann Urol (Paris), 1999. 33: 369. https://www.ncbi.nlm.nih.gov/pubmed/10544742
778. Castagnetti, M., *et al.* Management of duplex system ureteroceles in neonates and infants. Nat Rev Urol, 2009. 6: 307. https://www.ncbi.nlm.nih.gov/pubmed/19498409
779. Han, M.Y., *et al.* Indications for nonoperative management of ureteroceles. J Urol, 2005. 174: 1652. https://www.ncbi.nlm.nih.gov/pubmed/16148674
780. Mariyappa, B., *et al.* Management of duplex-system ureterocele. J Paediatr Child Health, 2014. 50: 96. https://www.ncbi.nlm.nih.gov/pubmed/24372828
781. Adorisio, O., *et al.* Effectiveness of primary endoscopic incision in treatment of ectopic ureterocele associated with duplex system. Urology, 2011. 77: 191. https://www.ncbi.nlm.nih.gov/pubmed/21168903
782. DeFoor, W., *et al.* Ectopic ureterocele: clinical application of classification based on renal unit jeopardy. J Urol, 2003. 169: 1092. https://www.ncbi.nlm.nih.gov/pubmed/12576859
783. Jayanthi, V.R., *et al.* Long-term outcome of transurethral puncture of ectopic ureteroceles: initial success and late problems. J Urol, 1999. 162: 1077. https://www.ncbi.nlm.nih.gov/pubmed/12187248
784. Jesus, L.E., *et al.* Clinical evolution of vesicoureteral reflux following endoscopic puncture in children with duplex system ureteroceles. J Urol, 2011. 186: 1455. https://www.ncbi.nlm.nih.gov/pubmed/21862045
785. Husmann, D.A., *et al.* Ureterocele associated with ureteral duplication and a nonfunctioning upper pole segment: management by partial nephroureterectomy alone. J Urol, 1995. 154: 723. https://www.ncbi.nlm.nih.gov/pubmed/7609163
786. el Ghoneimi, A., *et al.* Ectopic ureter with complete ureteric duplication: conservative surgical management. J Pediatr Surg, 1996. 31: 467. https://www.ncbi.nlm.nih.gov/pubmed/8801293
787. Smith, F.L., *et al.* Surgery for duplex kidneys with ectopic ureters: ipsilateral ureteroureterostomy versus polar nephrectomy. J Urol, 1989. 142: 532. https://www.ncbi.nlm.nih.gov/pubmed/2746774
788. Storm, D.W., *et al.* Laparoscopic ipsilateral ureteroureterostomy in the management of ureteral ectopia in infants and children. J Pediatr Urol, 2011. 7: 529. https://www.ncbi.nlm.nih.gov/pubmed/20869918
789. Herndon, C.D., *et al.* A complex urologic problem demonstrates how far pediatric urology has progressed. Conn Med, 1999. 63: 707. https://www.ncbi.nlm.nih.gov/pubmed/10659470
790. Jayanthi, V.R., *et al.* Bilateral single ureteral ectopia: difficulty attaining continence using standard bladder neck repair. J Urol, 1997. 158: 1933. https://www.ncbi.nlm.nih.gov/pubmed/9334642
791. Johnin, K., *et al.* Bilateral single ectopic ureters with hypoplastic bladder: how should we treat these challenging entities? J Pediatr Urol, 2007. 3: 243. https://www.ncbi.nlm.nih.gov/pubmed/18947744
792. Roy Choudhury, S., *et al.* Spectrum of ectopic ureters in children. Pediatr Surg Int, 2008. 24: 819. https://www.ncbi.nlm.nih.gov/pubmed/18463883
793. Lee, P.A., *et al.* Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics, 2006. 118: e488. https://www.ncbi.nlm.nih.gov/pubmed/16882788
794. Houk, C.P., *et al.* Summary of consensus statement on intersex disorders and their management. International Intersex Consensus Conference. Pediatrics, 2006. 118: 753. https://www.ncbi.nlm.nih.gov/pubmed/16882833
795. Maggi, M., *et al.* Standard operating procedures: pubertas tarda/delayed puberty--male. J Sex Med, 2013. 10: 285. https://www.ncbi.nlm.nih.gov/pubmed/22376050
796. Wales, J.K. Disordered pubertal development. Arch Dis Child Educ Pract Ed, 2012. 97: 9. https://www.ncbi.nlm.nih.gov/pubmed/21278425

797. Feldman, K.W., *et al.* Fetal phallic growth and penile standards for newborn male infants. J Pediatr, 1975. 86: 395.
https://www.ncbi.nlm.nih.gov/pubmed/1113226
798. Aaronson, I.A. Micropenis: medical and surgical implications. J Urol, 1994. 152: 4.
https://www.ncbi.nlm.nih.gov/pubmed/8201683
799. Gonzales, J.R. Micropenis. AUA Update Series. 1983. 2. [No abstract available].
800. Choi, S.K., *et al.* Transdermal dihydrotestosterone therapy and its effects on patients with microphallus. J Urol, 1993. 150: 657.
https://www.ncbi.nlm.nih.gov/pubmed/8326617
801. Burstein, S., *et al.* Early determination of androgen-responsiveness is important in the management of microphallus. Lancet, 1979. 2: 983.
https://www.ncbi.nlm.nih.gov/pubmed/91775
802. Diamond, M. Pediatric management of ambiguous and traumatized genitalia. J Urol, 1999. 162: 1021.
https://www.ncbi.nlm.nih.gov/pubmed/10458424
803. Bin-Abbas, B., *et al.* Congenital hypogonadotropic hypogonadism and micropenis: effect of testosterone treatment on adult penile size why sex reversal is not indicated. J Pediatr, 1999. 134: 579.
https://www.ncbi.nlm.nih.gov/pubmed/10228293
804. Calikoglu, A.S. Should boys with micropenis be reared as girls? J Pediatr, 1999. 134: 537.
https://www.ncbi.nlm.nih.gov/pubmed/10228285
805. Creighton, S., *et al.* Medical photography: ethics, consent and the intersex patient. BJU Int, 2002. 89: 67.
https://www.ncbi.nlm.nih.gov/pubmed/11849163
806. Wright, N.B., *et al.* Imaging children with ambiguous genitalia and intersex states. Clin Radiol, 1995. 50: 823.
https://www.ncbi.nlm.nih.gov/pubmed/8536391
807. Biswas, K., *et al.* Imaging in intersex disorders. J Pediatr Endocrinol Metab, 2004. 17: 841.
https://www.ncbi.nlm.nih.gov/pubmed/15270401
808. Denes, F.T., *et al.* Laparoscopic management of intersexual states. Urol Clin North Am, 2001. 28: 31.
https://www.ncbi.nlm.nih.gov/pubmed/11277066
809. Chertin, B., *et al.* The use of laparoscopy in intersex patients. Pediatr Surg Int, 2006. 22: 405.
https://www.ncbi.nlm.nih.gov/pubmed/16521001
810. Timing of elective surgery on the genitalia of male children with particular reference to the risks, benefits, and psychological effects of surgery and anesthesia. American Academy of Pediatrics. Pediatrics, 1996. 97: 590.
http://pediatrics.aappublications.org/content/97/4/590
811. Mouriquand, P., *et al.* The ESPU/SPU standpoint on the surgical management of Disorders of Sex Development (DSD). J Pediatr Urol, 2014. 10: 8.
https://www.ncbi.nlm.nih.gov/pubmed/24528671
812. Creighton, S.M. Adult female outcomes of feminising surgery for ambiguous genitalia. Pediatr Endocrinol Rev, 2004. 2: 199.
https://www.ncbi.nlm.nih.gov/pubmed/16429106
813. Minto, C.L., *et al.* The effect of clitoral surgery on sexual outcome in individuals who have intersex conditions with ambiguous genitalia: a cross-sectional study. Lancet, 2003. 361: 1252.
https://www.ncbi.nlm.nih.gov/pubmed/12699952
814. Crouch, N.S., *et al.* Minimal surgical intervention in the management of intersex conditions. J Pediatr Endocrinol Metab, 2004. 17: 1591.
https://www.ncbi.nlm.nih.gov/pubmed/15645692
815. Jenak, R., *et al.* Total urogenital sinus mobilization: a modified perineal approach for feminizing genitoplasty and urogenital sinus repair. J Urol, 2001. 165: 2347.
https://www.ncbi.nlm.nih.gov/pubmed/11371975
816. Leclair, M.D., *et al.* The surgical outcome of total urogenital mobilization for cloacal repair. J Urol, 2007. 177: 1492.
https://www.ncbi.nlm.nih.gov/pubmed/17382761
817. Schober, J.M. Feminizing genitoplasty: a synopsis of issues relating to genital surgery in intersex individuals. J Pediatr Endocrinol Metab, 2004. 17: 697.
https://www.ncbi.nlm.nih.gov/pubmed/15237702

818. Cools, M., *et al.* Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. Endocr Rev, 2006. 27: 468.
https://www.ncbi.nlm.nih.gov/pubmed/16735607
819. Heikkila, J., *et al.* Long-term risk of end stage renal disease in patients with posterior urethral valves. J Urol, 2011. 186: 2392.
https://www.ncbi.nlm.nih.gov/pubmed/22014822
820. Reinberg, Y., *et al.* Influence of initial therapy on progression of renal failure and body growth in children with posterior urethral valves. J Urol, 1992. 148: 532.
https://www.ncbi.nlm.nih.gov/pubmed/1640516
821. Smith, G.H., *et al.* The long-term outcome of posterior urethral valves treated with primary valve ablation and observation. J Urol, 1996. 155: 1730.
https://www.ncbi.nlm.nih.gov/pubmed/8627873
822. Atwell, J.D. Posterior urethral valves in the British Isles: a multicenter B.A.P.S. review. J Pediatr Surg, 1983. 18: 70.
https://www.ncbi.nlm.nih.gov/pubmed/6834230
823. Casale, A.J. Early ureteral surgery for posterior urethral valves. Urol Clin North Am, 1990. 17: 361.
https://www.ncbi.nlm.nih.gov/pubmed/2186541
824. Cromie, W.J., *et al.* Implications of prenatal ultrasound screening in the incidence of major genitourinary malformations. J Urol, 2001. 165: 1677.
https://www.ncbi.nlm.nih.gov/pubmed/11342955
825. Dewan, P.A., *et al.* Endoscopic reappraisal of the morphology of congenital obstruction of the posterior urethra. Br J Urol, 1992. 70: 439.
https://www.ncbi.nlm.nih.gov/pubmed/1450856
826. Young, H.H., *et al.* Congenital obstruction of the posterior urethra. J Urol, 3: 289-365, 1919. J Urol, 2002. 167: 265.
https://www.ncbi.nlm.nih.gov/pubmed/11743334
827. Rosenfeld, B., *et al.* Type III posterior urethral valves: presentation and management. J Pediatr Surg, 1994. 29: 81.
https://www.ncbi.nlm.nih.gov/pubmed/8120770
828. Stephens, F.D., *et al.* Pathogenesis of the prune belly syndrome. J Urol, 1994. 152: 2328.
https://www.ncbi.nlm.nih.gov/pubmed/7966734
829. Bernardes, L.S., *et al.* Keyhole sign: how specific is it for the diagnosis of posterior urethral valves? Ultrasound Obstet Gynecol, 2009. 34: 419.
https://www.ncbi.nlm.nih.gov/pubmed/19642115
830. Churchill, B.M., *et al.* Emergency treatment and long-term follow-up of posterior urethral valves. Urol Clin North Am, 1990. 17: 343.
https://www.ncbi.nlm.nih.gov/pubmed/2186540
831. Hoover, D.L., *et al.* Posterior urethral valves, unilateral reflux and renal dysplasia: a syndrome. J Urol, 1982. 128: 994.
https://www.ncbi.nlm.nih.gov/pubmed/7176067
832. Rittenberg, M.H., *et al.* Protective factors in posterior urethral valves. J Urol, 1988. 140: 993.
https://www.ncbi.nlm.nih.gov/pubmed/3139895
833. Cuckow, P.M., *et al.* Long-term renal function in the posterior urethral valves, unilateral reflux and renal dysplasia syndrome. J Urol, 1997. 158: 1004.
https://www.ncbi.nlm.nih.gov/pubmed/9258130
834. Kleppe, S., *et al.* Impact of prenatal urinomas in patients with posterior urethral valves and postnatal renal function. J Perinat Med, 2006. 34: 425.
https://www.ncbi.nlm.nih.gov/pubmed/16965232
835. Dinneen, M.D., *et al.* Antenatal diagnosis of posterior urethral valves. Br J Urol, 1993. 72: 364.
https://www.ncbi.nlm.nih.gov/pubmed/8220998
836. Freedman, A.L., *et al.* Fetal therapy for obstructive uropathy: past, present.future? Pediatr Nephrol, 2000. 14: 167.
https://www.ncbi.nlm.nih.gov/pubmed/10684370
837. McLorie, G., *et al.* Outcome analysis of vesicoamniotic shunting in a comprehensive population. J Urol, 2001. 166: 1036.
https://www.ncbi.nlm.nih.gov/pubmed/11490292
838. Salam, M.A. Posterior urethral valve: Outcome of antenatal intervention. Int J Urol, 2006. 13: 1317.
https://www.ncbi.nlm.nih.gov/pubmed/17010011

839. Morris, R.K., *et al.* Percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): a randomised trial. Lancet, 2013. 382: 1496. https://www.ncbi.nlm.nih.gov/pubmed/23953766
840. Morris, R.K., *et al.* A systematic review and meta-analysis of the effectiveness of fetal cystocopy as an intervention for congenital bladder neck obstruction. Repr Sciences 2011. 18: 366A. http://fn.bmj.com/content/96/Suppl_1/Fa61.2.abstract
841. Martinez, J.M., *et al.* Laser ablation of posterior urethral valves by fetal cystoscopy. Fetal Diagn Ther, 2015. 37: 267. https://www.ncbi.nlm.nih.gov/pubmed/25614247
842. Babu, R., *et al.* Early outcome following diathermy versus cold knife ablation of posterior urethral valves. J Pediatr Urol, 2013. 9: 7. https://www.ncbi.nlm.nih.gov/pubmed/22417679
843. Shirazi, M., *et al.* Which patients are at higher risk for residual valves after posterior urethral valve ablation? Korean J Urol, 2014. 55: 64. https://www.ncbi.nlm.nih.gov/pubmed/24466400
844. Krahn, C.G., *et al.* Cutaneous vesicostomy in the young child: indications and results. Urology, 1993. 41: 558. https://www.ncbi.nlm.nih.gov/pubmed/8516992
845. Kim, Y.H., *et al.* Comparative urodynamic findings after primary valve ablation, vesicostomy or proximal diversion. J Urol, 1996. 156: 673. https://www.ncbi.nlm.nih.gov/pubmed/8683757
846. Podesta, M., *et al.* Bladder function associated with posterior urethral valves after primary valve ablation or proximal urinary diversion in children and adolescents. J Urol, 2002. 168: 1830. https://www.ncbi.nlm.nih.gov/pubmed/12352370
847. Novak, M.E., *et al.* Single-stage reconstruction of urinary tract after loop cutaneous ureterostomy. Urology, 1978. 11: 134. https://www.ncbi.nlm.nih.gov/pubmed/628990
848. Sober, I. Pelvioureterostomy-en-Y. J Urol, 1972. 107: 473. https://www.ncbi.nlm.nih.gov/pubmed/5010719
849. Williams, D.I., *et al.* Ring ureterostomy. Br J Urol, 1975. 47: 789. https://www.ncbi.nlm.nih.gov/pubmed/1222345
850. Scott, J.E. Management of congenital posterior urethral valves. Br J Urol, 1985. 57: 71. https://www.ncbi.nlm.nih.gov/pubmed/3971107
851. Mukherjee, S., *et al.* What is the effect of circumcision on risk of urinary tract infection in boys with posterior urethral valves? J Pediatr Surg, 2009. 44: 417. https://www.ncbi.nlm.nih.gov/pubmed/19231547
852. Cozzi, D.A., *et al.* Posterior urethral valves: relationship between vesicoureteral reflux and renal function. Urology, 2011. 77: 1209. https://www.ncbi.nlm.nih.gov/pubmed/21109298
853. Bellinger, M.F. Ureterocystoplasty: a unique method for vesical augmentation in children. J Urol, 1993. 149: 811. https://www.ncbi.nlm.nih.gov/pubmed/8455246
854. Misseri, R., *et al.* Myogenic failure in posterior urethral valve disease: real or imagined? J Urol, 2002. 168: 1844. https://www.ncbi.nlm.nih.gov/pubmed/12352373
855. Kim, Y.H., *et al.* Management of posterior urethral valves on the basis of urodynamic findings. J Urol, 1997. 158: 1011. https://www.ncbi.nlm.nih.gov/pubmed/9258132
856. Abraham, M.K., *et al.* Role of alpha adrenergic blocker in the management of posterior urethral valves. Pediatr Surg Int, 2009. 25: 1113. https://www.ncbi.nlm.nih.gov/pubmed/19727771
857. Skenazy, J., *et al.* 1618 Alpha adrenergic blockade in neonates with posterior urethral valves. J Urol, 2012. 187: e654. http://www.sciencedirect.com/science/article/pii/S0022534712017752
858. DeFoor, W., *et al.* Risk factors for end stage renal disease in children with posterior urethral valves. J Urol, 2008. 180: 1705. https://www.ncbi.nlm.nih.gov/pubmed/18708224
859. Kamal, M.M., *et al.* Impact of posterior urethral valves on pediatric renal transplantation: a single-center comparative study of 297 cases. Pediatr Transplant, 2011. 15: 482. https://www.ncbi.nlm.nih.gov/pubmed/21599816

860. Fine, M.S., *et al.* Posterior urethral valve treatments and outcomes in children receiving kidney transplants. J Urol, 2011. 185: 2507.
https://www.ncbi.nlm.nih.gov/pubmed/21527196
861. Salomon, L., *et al.* Role of the bladder in delayed failure of kidney transplants in boys with posterior urethral valves. J Urol, 2000. 163: 1282.
https://www.ncbi.nlm.nih.gov/pubmed/10737529
862. McAninch, J.W., *et al.* Renal reconstruction after injury. J Urol, 1991. 145: 932.
https://www.ncbi.nlm.nih.gov/pubmed/2016804
863. McAleer, I.M., *et al.* Genitourinary trauma in the pediatric patient. Urology, 1993. 42: 563.
https://www.ncbi.nlm.nih.gov/pubmed/8236601
864. Miller, R.C., *et al.* The incidental discovery of occult abdominal tumors in children following blunt abdominal trauma. J Trauma, 1966. 6: 99.
https://www.ncbi.nlm.nih.gov/pubmed/5901856
865. Moore, E.E., *et al.* Organ injury scaling: spleen, liver, and kidney. J Trauma, 1989. 29: 1664.
https://www.ncbi.nlm.nih.gov/pubmed/2593197
866. Stalker, H.P., *et al.* The significance of hematuria in children after blunt abdominal trauma. AJR Am J Roentgenol, 1990. 154: 569.
https://www.ncbi.nlm.nih.gov/pubmed/2106223
867. Mee, S.L., *et al.* Radiographic assessment of renal trauma: a 10-year prospective study of patient selection. J Urol, 1989. 141: 1095.
https://www.ncbi.nlm.nih.gov/pubmed/2709493
868. Stein, J.P., *et al.* Blunt renal trauma in the pediatric population: indications for radiographic evaluation. Urology, 1994. 44: 406.
https://www.ncbi.nlm.nih.gov/pubmed/8073555
869. Carpio, F., *et al.* Radiographic staging of renal injuries. World J Urol, 1999. 17: 66.
https://www.ncbi.nlm.nih.gov/pubmed/10367363
870. Radmayr, C., *et al.* Blunt renal trauma in children: 26 years clinical experience in an alpine region. Eur Urol, 2002. 42: 297.
https://www.ncbi.nlm.nih.gov/pubmed/12234516
871. Presti, J.C., Jr., *et al.* Ureteral and renal pelvic injuries from external trauma: diagnosis and management. J Trauma, 1989. 29: 370.
https://www.ncbi.nlm.nih.gov/pubmed/2926851
872. Mulligan, J.M., *et al.* Ureteropelvic junction disruption secondary to blunt trauma: excretory phase imaging (delayed films) should help prevent a missed diagnosis. J Urol, 1998. 159: 67.
https://www.ncbi.nlm.nih.gov/pubmed/9400439
873. al-Ali, M., *et al.* The late treatment of 63 overlooked or complicated ureteral missile injuries: the promise of nephrostomy and role of autotransplantation. J Urol, 1996. 156: 1918.
https://www.ncbi.nlm.nih.gov/pubmed/8911355
874. Fernandez Fernandez, A., *et al.* Blunt traumatic rupture of the high right ureter, repaired with appendix interposition. Urol Int, 1994. 53: 97.
https://www.ncbi.nlm.nih.gov/pubmed/7801425
875. Sivit, C.J., *et al.* CT diagnosis and localization of rupture of the bladder in children with blunt abdominal trauma: significance of contrast material extravasation in the pelvis. AJR Am J Roentgenol, 1995. 164: 1243.
https://www.ncbi.nlm.nih.gov/pubmed/7717239
876. Hochberg, E., *et al.* Bladder rupture associated with pelvic fracture due to blunt trauma. Urology, 1993. 41: 531.
https://www.ncbi.nlm.nih.gov/pubmed/8516988
877. Haas, C.A., *et al.* Limitations of routine spiral computerized tomography in the evaluation of bladder trauma. J Urol, 1999. 162: 51.
https://www.ncbi.nlm.nih.gov/pubmed/10379738
878. Volpe, M.A., *et al.* Is there a difference in outcome when treating traumatic intraperitoneal bladder rupture with or without a suprapubic tube? J Urol, 1999. 161: 1103.
https://www.ncbi.nlm.nih.gov/pubmed/10081847
879. Richardson, J.R., Jr., *et al.* Non-operative treatment of the ruptured bladder. J Urol, 1975. 114: 213.
https://www.ncbi.nlm.nih.gov/pubmed/1159910
880. Cass, A.S., *et al.* Urethral injury due to external trauma. Urology, 1978. 11: 607.
https://www.ncbi.nlm.nih.gov/pubmed/675928
881. Pokorny, M., *et al.* Urological injuries associated with pelvic trauma. J Urol, 1979. 121: 455.
https://www.ncbi.nlm.nih.gov/pubmed/439217

882. Elliott, D.S., *et al.* Long-term followup and evaluation of primary realignment of posterior urethral disruptions. J Urol, 1997. 157: 814.
https://www.ncbi.nlm.nih.gov/pubmed/9072573
883. Boone, T.B., *et al.* Postpubertal genitourinary function following posterior urethral disruptions in children. J Urol, 1992. 148: 1232.
https://www.ncbi.nlm.nih.gov/pubmed/1404642
884. Koraitim, M.M. Posttraumatic posterior urethral strictures in children: a 20-year experience. J Urol, 1997. 157: 641.
https://www.ncbi.nlm.nih.gov/pubmed/8996388
885. Avanoglu, A., *et al.* Posterior urethral injuries in children. Br J Urol, 1996. 77: 597.
https://www.ncbi.nlm.nih.gov/pubmed/8777627
886. Nair, S.G., *et al.* Perioperative fluid and electrolyte management in pediatric patients. Indian J Anaesth, 2004. 48: 355.
http://medind.nic.in/iad/t04/i5/iadt04i5p355.pdf
887. Imura, K., *et al.* Perioperative nutrition and metabolism in pediatric patients. World J Surg, 2000. 24: 1498.
https://www.ncbi.nlm.nih.gov/pubmed/11193714
888. Ward Platt, M.P., *et al.* The effects of anesthesia and surgery on metabolic homeostasis in infancy and childhood. J Pediatr Surg, 1990. 25: 472.
https://www.ncbi.nlm.nih.gov/pubmed/2191106
889. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: a report by the American Society of Anesthesiologist Task Force on Preoperative Fasting. Anesthesiology, 1999. 90: 896.
https://www.ncbi.nlm.nih.gov/pubmed/10078693
890. Murat, I., *et al.* Perioperative fluid therapy in pediatrics. Paediatr Anaesth, 2008. 18: 363.
https://www.ncbi.nlm.nih.gov/pubmed/18312509
891. Redfern, N., *et al.* Blood glucose in anaesthetised children. Comparison of blood glucose concentrations in children fasted for morning and afternoon surgery. Anaesthesia, 1986. 41: 272.
https://www.ncbi.nlm.nih.gov/pubmed/3963330
892. Leelanukrom, R., *et al.* Intraoperative fluid and glucose management in children. Paediatr Anaesth, 2000. 10: 353.
https://www.ncbi.nlm.nih.gov/pubmed/10886690
893. Holliday, M.A., *et al.* The maintenance need for water in parenteral fluid therapy. Pediatrics, 1957. 19: 823.
https://www.ncbi.nlm.nih.gov/pubmed/13431307
894. Lindahl, S.G. Energy expenditure and fluid and electrolyte requirements in anesthetized infants and children. Anesthesiology, 1988. 69: 377.
https://www.ncbi.nlm.nih.gov/pubmed/3415017
895. Bailey, A.G., *et al.* Perioperative crystalloid and colloid fluid management in children: where are we and how did we get here? Anesth Analg, 2010. 110: 375.
https://www.ncbi.nlm.nih.gov/pubmed/19955503
896. Furman, E.B., *et al.* Specific therapy in water, electrolyte and blood-volume replacement during pediatric surgery. Anesthesiology, 1975. 42: 187.
https://www.ncbi.nlm.nih.gov/pubmed/1115368
897. Berry, F., Practical aspects of fluid and electrolyte therapy, in Anesthetic Management of Difficult and Routine Pediatric Patients,1986, Churchill Livingstone: New York.
898. Kearney, R., *et al.* Withholding oral fluids from children undergoing day surgery reduces vomiting. Paediatr Anaesth, 1998. 8: 331.
https://www.ncbi.nlm.nih.gov/pubmed/9672932
899. Goodarzi, M., *et al.* A prospective randomized blinded study of the effect of intravenous fluid therapy on postoperative nausea and vomiting in children undergoing strabismus surgery. Paediatr Anaesth, 2006. 16: 49.
https://www.ncbi.nlm.nih.gov/pubmed/16409529
900. Moritz, M.L., *et al.* Intravenous fluid management for the acutely ill child. Curr Opin Pediatr, 2011. 23: 186.
https://www.ncbi.nlm.nih.gov/pubmed/21415832
901. Yung, M., *et al.* Randomised controlled trial of intravenous maintenance fluids. J Paediatr Child Health, 2009. 45: 9.
https://www.ncbi.nlm.nih.gov/pubmed/18036144

902. Duke, T., *et al.* Intravenous fluids for seriously ill children: time to reconsider. Lancet, 2003. 362: 1320.
https://www.ncbi.nlm.nih.gov/pubmed/14575980
903. Greenbaum, L., The pathophysiology of body fluids and fluid therapy, in Kliegman: Nelson textbook of pediatrics, 2007, Saunders Elsevier: Philadelphia, PA.
904. Holliday, M.A., *et al.* Fluid therapy for children: facts, fashions and questions. Arch Dis Child, 2007. 92: 546.
https://www.ncbi.nlm.nih.gov/pubmed/17175577
905. Moritz, M.L., *et al.* Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. Pediatrics, 2003. 111: 227.
https://www.ncbi.nlm.nih.gov/pubmed/12563043
906. Messner, A.H., *et al.* Oral fluid intake following tonsillectomy. Int J Pediatr Otorhinolaryngol, 1997. 39: 19.
https://www.ncbi.nlm.nih.gov/pubmed/9051436
907. Schreiner, M.S., *et al.* Should children drink before discharge from day surgery? Anesthesiology, 1992. 76: 528.
https://www.ncbi.nlm.nih.gov/pubmed/1550277
908. Radke, O.C., *et al.* The effect of postoperative fasting on vomiting in children and their assessment of pain. Paediatr Anaesth, 2009. 19: 494.
https://www.ncbi.nlm.nih.gov/pubmed/19453581
909. Cheng, W., *et al.* Electrogastrographic changes in children who undergo day-surgery anesthesia. J Pediatr Surg, 1999. 34: 1336.
https://www.ncbi.nlm.nih.gov/pubmed/10507424
910. Mercan, A., *et al.* The effect of timing and temperature of oral fluids ingested after minor surgery in preschool children on vomiting: a prospective, randomized, clinical study. Paediatr Anaesth, 2011. 21: 1066.
https://www.ncbi.nlm.nih.gov/pubmed/21668799
911. Everett, L.L. Pain management for pediatric ambulatory anesthesia. Curr Opin Anaesthesiol, 2002. 15: 609.
https://www.ncbi.nlm.nih.gov/pubmed/17019260
912. Bozkurt, P. The analgesic efficacy and neuroendocrine response in paediatric patients treated with two analgesic techniques: using morphine-epidural and patient-controlled analgesia. Paediatr Anaesth, 2002. 12: 248.
https://www.ncbi.nlm.nih.gov/pubmed/11903939
913. Gehdoo, R.P. Postoperative pain management in pediatric patients. Indian J Anesth 2004. 48: 406.
http://medind.nic.in/iad/t04/i5/iadt04i5p406.pdf
914. Arana, A., *et al.* Treatment with paracetamol in infants. Acta Anaesthesiol Scand, 2001. 45: 20.
https://www.ncbi.nlm.nih.gov/pubmed/11152028
915. Messerer, B., *et al.* Implementation of a standardized pain management in a pediatric surgery unit. Pediatr Surg Int, 2010. 26: 879.
https://www.ncbi.nlm.nih.gov/pubmed/20625751
916. Verghese, S.T., *et al.* Acute pain management in children. J Pain Res, 2010. 3: 105.
https://www.ncbi.nlm.nih.gov/pubmed/21197314
917. Ivani, G., *et al.* Postoperative analgesia in infants and children: new developments. Minerva Anestesiol, 2004. 70: 399.
https://www.ncbi.nlm.nih.gov/pubmed/15181422
918. Karling, M., *et al.* Acute and postoperative pain in children: a Swedish nationwide survey. Acta Paediatr, 2002. 91: 660.
https://www.ncbi.nlm.nih.gov/pubmed/12162598
919. Stamer, U.M., *et al.* Postoperative analgesia in children--current practice in Germany. Eur J Pain, 2005. 9: 555.
https://www.ncbi.nlm.nih.gov/pubmed/16139184
920. Taylor, B.J., *et al.* Assessing postoperative pain in neonates: a multicenter observational study. Pediatrics, 2006. 118: e992.
https://www.ncbi.nlm.nih.gov/pubmed/17015519
921. Prevention and management of pain and stress in the neonate. American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee. Pediatrics, 2000. 105: 454.
https://www.ncbi.nlm.nih.gov/pubmed/10654977

922. Anand, K.J. Consensus statement for the prevention and management of pain in the newborn. Arch Pediatr Adolesc Med, 2001. 155: 173.
https://www.ncbi.nlm.nih.gov/pubmed/11177093
923. Simons, S.H., *et al.* Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. Arch Pediatr Adolesc Med, 2003. 157: 1058.
https://www.ncbi.nlm.nih.gov/pubmed/14609893
924. Taddio, A., *et al.* Effect of neonatal circumcision on pain response during subsequent routine vaccination. Lancet, 1997. 349: 599.
https://www.ncbi.nlm.nih.gov/pubmed/9057731
925. Grunau, R.E., *et al.* Demographic and therapeutic determinants of pain reactivity in very low birth weight neonates at 32 Weeks' postconceptional Age. Pediatrics, 2001. 107: 105.
https://www.ncbi.nlm.nih.gov/pubmed/11134442
926. Kain, Z.N., *et al.* Preoperative anxiety, postoperative pain, and behavioral recovery in young children undergoing surgery. Pediatrics, 2006. 118: 651.
https://www.ncbi.nlm.nih.gov/pubmed/16882820
927. Young, K.D. Pediatric procedural pain. Ann Emerg Med, 2005. 45: 160.
https://www.ncbi.nlm.nih.gov/pubmed/15671974
928. Ghai, B., *et al.* Postoperative pain assessment in preverbal children and children with cognitive impairment. Paediatr Anaesth, 2008. 18: 462.
https://www.ncbi.nlm.nih.gov/pubmed/18363630
929. Ellis, J.A., *et al.* Evaluation of a continuous epidural analgesia program for postoperative pain in children. Pain Manag Nurs, 2007. 8: 146.
https://www.ncbi.nlm.nih.gov/pubmed/18036502
930. Schecter, W.P., *et al.* Special considerations in perioperative pain management: audiovisual distraction, geriatrics, pediatrics, and pregnancy. J Am Coll Surg, 2005. 201: 612.
https://www.ncbi.nlm.nih.gov/pubmed/16183502
931. Jonas, D.A. Parent's management of their child's pain in the home following day surgery. J Child Health Care, 2003. 7: 150.
https://www.ncbi.nlm.nih.gov/pubmed/14516009
932. Kankkunen, P., *et al.* Families' and children's postoperative pain--literature review. J Pediatr Nurs, 2004. 19: 133.
https://www.ncbi.nlm.nih.gov/pubmed/15077212
933. Birmingham, P.K., *et al.* Patient-controlled epidural analgesia in children: can they do it? Anesth Analg, 2003. 96: 686.
https://www.ncbi.nlm.nih.gov/pubmed/12598244
934. Woolf, C.J., *et al.* Preemptive analgesia--treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg, 1993. 77: 362.
https://www.ncbi.nlm.nih.gov/pubmed/8346839
935. Kehlet, H., *et al.* The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg, 1993. 77: 1048.
https://www.ncbi.nlm.nih.gov/pubmed/8105724
936. World Health Organization, Cancer Pain Relief and Palliative Care in Children. 1998, World Health Organization: Geneva.
http://apps.who.int/iris/bitstream/10665/42001/1/9241545127.pdf
937. Anand, K.J., *et al.* Analgesia and local anesthesia during invasive procedures in the neonate. Clin Ther, 2005. 27: 844.
https://www.ncbi.nlm.nih.gov/pubmed/16117989
938. Yawman, D., *et al.* Pain relief for neonatal circumcision: a follow-up of residency training practices. Ambul Pediatr, 2006. 6: 210.
https://www.ncbi.nlm.nih.gov/pubmed/16843252
939. Choi, W.Y., *et al.* EMLA cream versus dorsal penile nerve block for postcircumcision analgesia in children. Anesth Analg, 2003. 96: 396.
https://www.ncbi.nlm.nih.gov/pubmed/12538184
940. Lehr, V.T., *et al.* Lidocaine 4% cream compared with lidocaine 2.5% and prilocaine 2.5% or dorsal penile block for circumcision. Am J Perinatol, 2005. 22: 231.
https://www.ncbi.nlm.nih.gov/pubmed/16041631
941. Matsota, P., *et al.* Intraoperative and postoperative analgesia with subcutaneous ring block of the penis with levobupivacaine for circumcision in children. Eur J Pediatr Surg, 2004. 14: 198.
https://www.ncbi.nlm.nih.gov/pubmed/15211412

942. Smith, D.P., *et al.* The efficacy of LMX versus EMLA for pain relief in boys undergoing office meatotomy. J Urol, 2004. 172: 1760.
https://www.ncbi.nlm.nih.gov/pubmed/15371808
943. Taddio, A., *et al.* A systematic review of lidocaine-prilocaine cream (EMLA) in the treatment of acute pain in neonates. Pediatrics, 1998. 101: E1.
https://www.ncbi.nlm.nih.gov/pubmed/9445511
944. Brady-Fryer, B., *et al.* Pain relief for neonatal circumcision. Cochrane Database Syst Rev, 2004: CD004217.
https://www.ncbi.nlm.nih.gov/pubmed/15495086
945. Sandeman, D.J., *et al.* A retrospective audit of three different regional anaesthetic techniques for circumcision in children. Anaesth Intensive Care, 2010. 38: 519.
https://www.ncbi.nlm.nih.gov/pubmed/20514962
946. Faraoni, D., *et al.* Does ultrasound guidance improve the efficacy of dorsal penile nerve block in children? Paediatr Anaesth, 2010. 20: 931.
https://www.ncbi.nlm.nih.gov/pubmed/20849498
947. Cyna, A.M., *et al.* Caudal epidural block versus other methods of postoperative pain relief for circumcision in boys. Cochrane Database Syst Rev, 2008: CD003005.
https://www.ncbi.nlm.nih.gov/pubmed/18843636
948. Margetts, L., *et al.* A comparison of caudal bupivacaine and ketamine with penile block for paediatric circumcision. Eur J Anaesthesiol, 2008. 25: 1009.
https://www.ncbi.nlm.nih.gov/pubmed/18652709
949. Weksler, N., *et al.* Is penile block better than caudal epidural block for postcircumcision analgesia? J Anesth, 2005. 19: 36.
https://www.ncbi.nlm.nih.gov/pubmed/
950. Gauntlett, I. A comparison between local anaesthetic dorsal nerve block and caudal bupivacaine with ketamine for paediatric circumcision. Paediatr Anaesth, 2003. 13: 38.
https://www.ncbi.nlm.nih.gov/pubmed/12535037
951. Sharpe, P., *et al.* Analgesia for circumcision in a paediatric population: comparison of caudal bupivacaine alone with bupivacaine plus two doses of clonidine. Paediatr Anaesth, 2001. 11: 695.
https://www.ncbi.nlm.nih.gov/pubmed/11696146
952. Beyaz, S.G. Comparison of Postoperative Analgesic Efficacy of Caudal Block versus Dorsal Penile Nerve Block with Levobupivacaine for Circumcision in Children. Korean J Pain, 2011. 24: 31.
https://www.ncbi.nlm.nih.gov/pubmed/21390176
953. Al-Zaben, K.R., *et al.* Intraoperative administration of dexmedetomidine reduces the analgesic requirements for children undergoing hypospadius surgery. Eur J Anaesthesiol, 2010. 27: 247.
https://www.ncbi.nlm.nih.gov/pubmed/19952754
954. Cho, J.E., *et al.* The addition of fentanyl to 1.5 mg/ml ropivacaine has no advantage for paediatric epidural analgesia. Acta Anaesthesiol Scand, 2009. 53: 1084.
https://www.ncbi.nlm.nih.gov/pubmed/19572930
955. Gunduz, M., *et al.* Comparison of caudal ketamine with lidocaine or tramadol administration for postoperative analgesia of hypospadias surgery in children. Paediatr Anaesth, 2006. 16: 158.
https://www.ncbi.nlm.nih.gov/pubmed/16430412
956. Silvani, P., *et al.* Caudal anesthesia in pediatrics: an update. Minerva Anestesiol, 2006. 72: 453.
https://www.ncbi.nlm.nih.gov/pubmed/16682915
957. Apiliogullari, S., *et al.* Efficacy of a low-dose spinal morphine with bupivacaine for postoperative analgesia in children undergoing hypospadias repair. Paediatr Anaesth, 2009. 19: 1078.
https://www.ncbi.nlm.nih.gov/pubmed/19708911
958. Laiq, N., *et al.* Comparison of caudal bupivacaine and bupivacaine-tramadol for postoperative analgesia in children undergoing hypospadias surgery. J Coll Physicians Surg Pak, 2009. 19: 678.
https://www.ncbi.nlm.nih.gov/pubmed/19889260
959. Gunes, Y., *et al.* Comparison of caudal vs intravenous tramadol administered either preoperatively or postoperatively for pain relief in boys. Paediatr Anaesth, 2004. 14: 324.
https://www.ncbi.nlm.nih.gov/pubmed/15078378
960. Hansen, T.G., *et al.* Caudal bupivacaine supplemented with caudal or intravenous clonidine in children undergoing hypospadias repair: a double-blind study. Br J Anaesth, 2004. 92: 223.
https://www.ncbi.nlm.nih.gov/pubmed/14722172
961. Thies, K.C., *et al.* Longer than expected-duration of caudal analgesia with two different doses of levobupivacaine in children undergoing hypospadias repair. J Pediatr Urol, 2010. 6: 585.
https://www.ncbi.nlm.nih.gov/pubmed/20171143

962. De Negri, P., *et al.* A comparison of epidural bupivacaine, levobupivacaine, and ropivacaine on postoperative analgesia and motor blockade. Anesth Analg, 2004. 99: 45. https://www.ncbi.nlm.nih.gov/pubmed/15281501
963. Ozbek, H., *et al.* The comparison of caudal ketamine, alfentanil and ketamine plus alfentanil administration for postoperative analgesia in children. Paediatr Anaesth, 2002. 12: 610. https://www.ncbi.nlm.nih.gov/pubmed/12358657
964. Bhardwaj, N., *et al.* Neostigmine does not prolong the duration of analgesia produced by caudal bupivacaine in children undergoing urethroplasty. J Postgrad Med, 2007. 53: 161. https://www.ncbi.nlm.nih.gov/pubmed/17699988
965. Ozyuvaci, E., *et al.* Evaluation of adding preoperative or postoperative rectal paracetamol to caudal bupivacaine for postoperative analgesia in children. Paediatr Anaesth, 2004. 14: 661. https://www.ncbi.nlm.nih.gov/pubmed/15283825
966. Samuel, M., *et al.* Prospective to a randomized double-blind controlled trial to assess efficacy of double caudal analgesia in hypospadias repair. J Pediatr Surg, 2002. 37: 168. https://www.ncbi.nlm.nih.gov/pubmed/11819193
967. Abdulatif, M., *et al.* Caudal neostigmine, bupivacaine, and their combination for postoperative pain management after hypospadias surgery in children. Anesth Analg, 2002. 95: 1215. https://www.ncbi.nlm.nih.gov/pubmed/12401596
968. Metzelder, M.L., *et al.* Penile block is associated with less urinary retention than caudal anesthesia in distal hypospadia repair in children. World J Urol, 2010. 28: 87. https://www.ncbi.nlm.nih.gov/pubmed/19466428
969. Chhibber, A.K., *et al.* Penile block timing for postoperative analgesia of hypospadias repair in children. J Urol, 1997. 158: 1156. https://www.ncbi.nlm.nih.gov/pubmed/9258161
970. Breschan, C., *et al.* A prospective study comparing the analgesic efficacy of levobupivacaine, ropivacaine and bupivacaine in pediatric patients undergoing caudal blockade. Paediatr Anaesth, 2005. 15: 301. https://www.ncbi.nlm.nih.gov/pubmed/15787921
971. Hong, J.Y., *et al.* Effect of dexamethasone in combination with caudal analgesia on postoperative pain control in day-case paediatric orchiopexy. Br J Anaesth, 2010. 105: 506. https://www.ncbi.nlm.nih.gov/pubmed/20659915
972. Taheri, R., *et al.* Efficacy of bupivacaine-neostigmine and bupivacaine-tramadol in caudal block in pediatric inguinal herniorrhaphy. Paediatr Anaesth, 2010. 20: 866. https://www.ncbi.nlm.nih.gov/pubmed/20716080
973. Fredrickson, M.J., *et al.* Improved analgesia with the ilioinguinal block compared to the transversus abdominis plane block after pediatric inguinal surgery: a prospective randomized trial. Paediatr Anaesth, 2010. 20: 1022. https://www.ncbi.nlm.nih.gov/pubmed/20964768
974. Jagannathan, N., *et al.* Unilateral groin surgery in children: will the addition of an ultrasound-guided ilioinguinal nerve block enhance the duration of analgesia of a single-shot caudal block? Paediatr Anaesth, 2009. 19: 892. https://www.ncbi.nlm.nih.gov/pubmed/19627532
975. Demiraran, Y., *et al.* Does tramadol wound infiltration offer an advantage over bupivacaine for postoperative analgesia in children following herniotomy? Paediatr Anaesth, 2006. 16: 1047. https://www.ncbi.nlm.nih.gov/pubmed/16972834
976. Machotta, A., *et al.* Comparison between instillation of bupivacaine versus caudal analgesia for postoperative analgesia following inguinal herniotomy in children. Paediatr Anaesth, 2003. 13: 397. https://www.ncbi.nlm.nih.gov/pubmed/12791112
977. Shenfeld, O., *et al.* Intraoperative irrigation with bupivacaine for analgesia after orchiopexy and herniorrhaphy in children. J Urol, 1995. 153: 185. https://www.ncbi.nlm.nih.gov/pubmed/7966769
978. Saeed, A., *et al.* Pain management for unilateral orchidopexy in children: an effective regimen. World J Surg, 2009. 33: 603. https://www.ncbi.nlm.nih.gov/pubmed/19115030
979. Tripi, P.A., *et al.* Clonidine increases duration of bupivacaine caudal analgesia for ureteroneocystostomy: a double-blind prospective trial. J Urol, 2005. 174: 1081. https://www.ncbi.nlm.nih.gov/pubmed/16094063
980. Merguerian, P.A., *et al.* Efficacy of continuous epidural analgesia versus single dose caudal analgesia in children after intravesical ureteroneocystostomy. J Urol, 2004. 172: 1621. https://www.ncbi.nlm.nih.gov/pubmed/15371775

981. Cain, M.P., *et al.* Continuous epidural anesthesia after ureteroneocystostomy in children. J Urol, 1995. 154: 791.
https://www.ncbi.nlm.nih.gov/pubmed/7609181
982. Hong, J.Y., *et al.* Fentanyl-sparing effect of acetaminophen as a mixture of fentanyl in intravenous parent-/nurse-controlled analgesia after pediatric ureteroneocystostomy. Anesthesiology, 2010. 113: 672.
https://www.ncbi.nlm.nih.gov/pubmed/20693884
983. Jo, Y.Y., *et al.* Ketorolac or fentanyl continuous infusion for post-operative analgesia in children undergoing ureteroneocystostomy. Acta Anaesthesiol Scand, 2011. 55: 54.
https://www.ncbi.nlm.nih.gov/pubmed/21083540
984. Miller, O.F., *et al.* Early hospital discharge for intravesical ureteroneocystostomy. J Urol, 2002. 167: 2556.
https://www.ncbi.nlm.nih.gov/pubmed/11992088
985. Park, J.M., *et al.* Ketorolac suppresses postoperative bladder spasms after pediatric ureteral reimplantation. Anesth Analg, 2000. 91: 11.
https://www.ncbi.nlm.nih.gov/pubmed/10866879
986. Routh, J.C., *et al.* Ketorolac is underutilized after ureteral reimplantation despite reduced hospital cost and reduced length of stay. Urology, 2010. 76: 9.
https://www.ncbi.nlm.nih.gov/pubmed/20138342
987. Kumar, R., *et al.* Dorsal lumbotomy incision for pediatric pyeloplasty--a good alternative. Pediatr Surg Int, 1999. 15: 562.
https://www.ncbi.nlm.nih.gov/pubmed/10631734
988. Piedrahita, Y.K., *et al.* Is one-day hospitalization after open pyeloplasty possible and safe? Urology, 2006. 67: 181.
https://www.ncbi.nlm.nih.gov/pubmed/16413360
989. Berta, E., *et al.* Single injection paravertebral block for renal surgery in children. Paediatr Anaesth, 2008. 18: 593.
https://www.ncbi.nlm.nih.gov/pubmed/18482238
990. Lonnqvist, P.A., *et al.* Paravertebral vs epidural block in children. Effects on postoperative morphine requirement after renal surgery. Acta Anaesthesiol Scand, 1994. 38: 346.
https://www.ncbi.nlm.nih.gov/pubmed/8067221
991. Ben-Meir, D., *et al.* Continuous epidural versus nonepidural analgesia for post-pyeloplasty pain in children. J Urol, 2009. 182: 1841.
https://www.ncbi.nlm.nih.gov/pubmed/19692062
992. Dingemann, J., *et al.* Perioperative analgesia strategies in fast-track pediatric surgery of the kidney and renal pelvis: lessons learned. World J Urol, 2010. 28: 215.
https://www.ncbi.nlm.nih.gov/pubmed/19565247
993. Freilich, D.A., *et al.* The effectiveness of aerosolized intraperitoneal bupivacaine in reducing postoperative pain in children undergoing robotic-assisted laparoscopic pyeloplasty. J Pediatr Urol, 2008. 4: 337.
https://www.ncbi.nlm.nih.gov/pubmed/18790415

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.