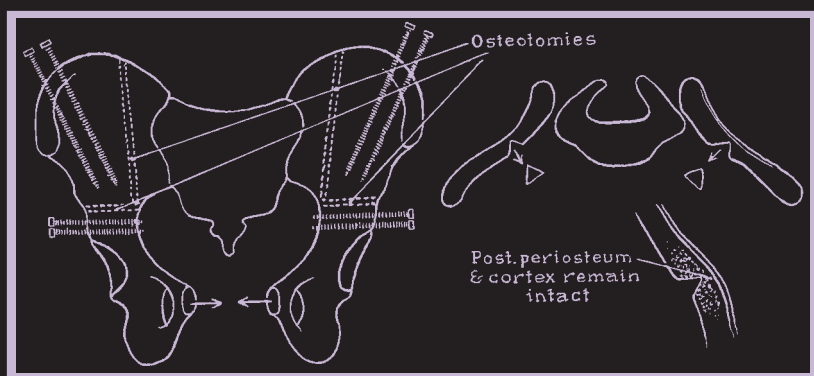

Pediatric Urology

Edited by

John P. Gearhart, MD, FAAP, FACS



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Edited by

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Preface

The practice and science of pediatric urology has changed rapidly in the last few years. New surgical techniques, better and more informative pre-natal evaluations, and better biomedical substances continue to arrive on the scene. *Pediatric Urology* offers a unique practice-oriented approach to these new developments offered by known experts in the field.

Pediatric Urology updates the reader on the modern evaluation of pre-natal hydronephrosis and compares the standard treatment of reflux with newer injectable techniques. The spectrum of treatment for hypospadias is described along with new developments in bladder exstrophy and what's new in the undescended testis. The evaluation of difficult duplication anomalies is described along with their treatment. A unique and very modern approach to voiding dysfunction and neurogenic bladders is presented in a quite logical and straightforward manner. Finally, pediatric stone disease and developmental problems associated with genitourinary defects are described.

We hope *Pediatric Urology* will show the practicing urologist in a clear, concise way where pediatric urology is going and how new discoveries are being applied in our field. Many thanks to our authors for taking time from their families, practices, residents, and research to share their expertise with our readers.

John P. Gearhart MD, FAAP, FACS

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1

Prenatal Diagnosis of Hydronephrosis

Marc Cendron, MD

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INTRODUCTION

Prenatal evaluation of the fetus goes back at least 30 years. The first report of fetal urologic anomaly diagnosed by ultrasound was published by Garrett et al. in 1970 (1). The overall incidence of detectable fetal anomalies is approx 1%; the incidence of urologic anomalies detected *in utero* is 1 in 500, and 50% of these are some form of urinary tract dilatation (2). Because the use of prenatal ultrasound screening has increased, the number of fetuses with known or suspected urinary tract abnormalities has also increased markedly during the last 20 years. With the increasing number of fetuses being diagnosed with abnormalities of the urinary tract, management has become more complex. The diagno-

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sis has an impact on the management of the pregnancy and has a significant effect on the emotional health of both parents.

Anxieties about the well-being of the child can grow as the pregnancy progresses. In addition, a significant number of the lesions identified may be obstructive, and earlier diagnosis, evaluation, and treatment can help to prevent renal damage. Finally, if a lethal condition such as high-grade obstruction causing major renal maldevelopment is found, pregnancy management can be modified. This chapter reviews the embryology and sonographic appearance of the developing fetal urinary tract and discusses many of the more common fetal urinary abnormalities encountered in clinical practice. The chapter concludes with a discussion of how ultrasonographic findings may influence obstetrical management, prenatal intervention and postnatal planning treatment, and eventual outcome.

A BRIEF EMBRYOLOGY OF THE URINARY TRACT

A thorough understanding of the embryologic development of the urinary tract is helpful in the interpretation of prenatally detected urologic abnormalities. The development of the urinary tract in the fetal period is complex and quite interesting. It results from the highly organized interaction of three germ-cell layers, from the migration of cells, and from the transformation of undifferentiated mesenchyma into physiologically active groups of cells. The molecular events involved are still being investigated. The primitive kidney system or mesonephros gives rise to the ureteral bud and lower urinary tract. During the fifth week of gestation, the ureteral bud elongates and penetrates an area of undifferentiated mesenchyma, which will become the metanephric blastema. Under inductive influences of the ureteral bud, the metanephric blastema differentiates into the excretory system of the kidney at about 7 wk of gestation. Urine production starts at about 9 to 10 wk of gestation. The kidneys and renal collecting system may be identified by ultrasound screening at about 11 wk of gestation (3). Any anomalous development of the urinary tract may result in renal agenesis, renal dysplasia (abnormal kidney tissue), multicystic dysplasia (large cysts as seen in the kidney), hypoplasia of the kidney, or anomalies of renal position. Such lesions may be readily identifiable by prenatal ultrasound starting as early as at about 10 wk of gestation.

When the kidney secretes urine, it passes down the ureters into the bladder and is excreted to form the amniotic fluid. Presence of amniotic fluid indicates both urine production by the kidney and good drainage of urine from the upper tract down through the lower tract.

Renal agenesis, absence of one or both kidneys, impacts variably on fetal viability. Clearly, bilateral renal agenesis is incompatible with life and will result in fetal demise. Renal agenesis is believed to occur after the development of the ureteral bud and may be caused by faulty interaction between the ureteral bud and metanephric blastema.

Renal dysplasia, a form of abnormal renal development, may be associated with an early obstructive process that may prevent normal drainage of the kidney. Obstruction is reported in as many as 50% of patients referred to a tertiary medical center. Furthermore, an ectopically located ureteral bud may induce only a portion or may induce an abnormal area of metanephric blastema, resulting in abnormal development of renal tissue. Multicystic dysplastic kidney (MCDK), a form of renal dysplasia, is usually seen in association with ureteral atresia or with an obstructive lesion at the ureteropelvic junction (UPJ). The timing of the obstructive process may influence the nature of the renal abnormality. Renal parenchyma may develop normally if the obstruction occurs later in gestation, causing only dilatation of the renal collecting system, some thinning of the renal parenchyma, and no distortion of the renal histology. The features of renal dysplasia caused by abnormal renal histology may be readily identified during the latter part of gestation (18 wk or later) by ultrasound. These features include increased ecogenicity, blurring of the corticomedullary junction, and distortion of the normal renal architecture.

Formation of the fetal bladder is a complex series of events involving the incorporation of the ureteral bud, the common excretory duct, and the interior portion of the cloaca into one functional structure. During the final phases of bladder development, migration and rotation of the ureteral bud cause the ureteral orifices to be located in the lateral position within the trigone. The bladder can be visualized by 10 wk of gestation (4). Vesicoureteral reflux is felt to result from abnormal location of the ureteral bud during its early incorporation into the bladder. The ureteral opening migrates more cranially and laterally, which causes the trigone to be wider and to lack muscular backing. The ureteral orifices occupy a very lateral position, which allows for a very short submucosal tunnel within the bladder. The diagnosis of reflux can be suggested prenatally by intermittent appearance of upper tract dilatation during bladder filling and emptying (5).

Abnormalities in the later development of the distal ureter located within the bladder may result in the formation of a ureterocele. The cause of a ureterocele has yet to be defined, but it represents a cystic dilatation of the distal ureter within the bladder and can be associated with ureteral duplication and concomitant obstruction of the upper pole and reflux in the lower pole of the ipsilateral kidney. Such lesions may

be identified prenatally as early as 18 to 20 wk of gestation. Very rarely, the ureterocele will prolapse into the urethra, causing bladder outlet obstruction in girls.

Obstruction of the distal ureter by an area of abnormal ureter at the level of the ureterovesical junction (UVJ) may also lead to massive dilatation of the ureter, which is then referred to as a megaureter. This is identifiable as a widely dilated, fluid-filled structure extending from the bladder up to the kidney. Anomalous development of the urethra may also lead to posterior urethral valves, which will cause bladder outlet obstruction, and massive dilatation of the bladder and the upper urinary tract may occur.

Finally, later in gestation, anomalies in fetal genitalia development can be observed by ultrasound. These findings may not affect the obstetric management of the fetus but clearly mandate postnatal follow-up. In addition, the normal development of the fetus depends greatly on the presence of amniotic fluid, which is produced by the kidneys later in gestation. Paucity of amniotic fluid caused by intrinsic renal abnormalities or obstructive uropathy results in pulmonary maldevelopment, pulmonary hypoplasia, and reduction in the size of the fetal thorax. These features can be readily identified by prenatal ultrasound.

EVALUATION OF THE NORMAL FETAL URINARY TRACT BY ULTRASOUND

As mentioned, fetal urine production begins late in the first trimester, and by the beginning of the second trimester urine can be readily detected in the fetal bladder. It is not until after about 16 wk of gestation that the fetal urinary tract contributes significantly to the amniotic fluid. The normal fetal bladder appears as a round or oval structure in the anterior fetal pelvis. Its size will change over time. Later in gestation, it will fill and empty approximately every 30 to 45 min. The change in size will help differentiate the fetal bladder from other cystic structures in the abdomen and pelvis. The wall of the normal bladder in the fetus is so thin that it is barely perceptible. The normal fetal ureters usually cannot be seen by sonography with the current technology. In general it is felt that not seeing the fetal urinary bladder early in gestation on an otherwise normal sonogram is of no clinical concern, but follow-up may be required to ensure that normal bladder filling and emptying is occurring.

In mothers with normal body habitus, the fetal kidneys can be seen as early as the second trimester, although frequently visualization is difficult because there is very little contrast between the fetal kidneys and the surrounding structures. As the pregnancy progresses and the

amount of peritoneal and retroperitoneal fat increases, the kidneys are more readily seen. The echogenic central renal sinus and the relatively sonolucent medullary pyramids also become more apparent as the gestational age increases. The fetal kidneys have an elliptical configuration along the long axis and a round-to-oval shape in the transverse plane. A lobulated contour is frequently appreciated. Severe oligohydramnios and maternal obesity are factors that diminish visualization of all fetal structures, including the kidneys. Standard measurements for renal length, width, thickness, and circumference have been reported as a function of gestational age by several authors, and a simple rule of thumb is to state that the renal length in millimeters is approximately equal to the gestational age of the fetus in weeks (6).

To detect and characterize fetal urinary tract abnormalities accurately, a systematic approach should be used. A number of sonographic parameters may be helpful in assessing the fetal urinary tract. One of these features is the amount of amniotic fluid present. If there is no evidence of ruptured membrane or intrauterine growth retardation but the amount of amniotic fluid is reduced (oligohydramnios), urinary tract abnormalities should be strongly suspected. The following should be considered: Is there evidence of urinary tract dilatation? What areas within the urinary tract are affected by the dilatation? Are there associated lesions such as urinary ascites? Can renal cysts be identified? Does the sonographic appearance of the kidneys show increased echogenicity? Associated anomalies may indicate the presence of a syndrome.

The first step in identifying urinary tract abnormalities generally involves assessment of amniotic fluid volume. Decreased urine output may result in oligohydramnios as early as 16 wk of gestation, when fetal urine begins to play a major role in the amount of fluid surrounding the fetus. Ultrasound assessment of the amniotic fluid is generally performed by subjective visual assessment or by amniotic fluid pocket measurement, the amniotic fluid index (7). Oligohydramnios in the second trimester is associated in general with poor prognosis because of associated pulmonary maldevelopment. Decreased amniotic fluid in the absence of premature rupture of membranes implies either decreased fetal urine output or obstruction to the flow of urine into or from the bladder. A very important consideration when evaluating suspected urinary tract abnormalities is whether the abnormality is unilateral or bilateral. Bilateral symmetrical abnormalities such as autosomal-recessive polycystic kidney disease often have a genetic cause. Unilateral abnormalities with a normal contralateral kidney generally have an excellent prognosis and do not warrant any extensive prenatal evalua-

tion. Dilatation of the renal collecting system is not always associated with obstruction and can be associated with reflux of urine from the bladder back up to the kidney. It should therefore not be assumed that a dilated renal collecting system is obstructed as documented by ultrasound. In addition, dilatation of the renal collecting system could be caused by an enlarged cyst, which would look like a dilated renal collecting system. It should be determined whether dilatation involves the entire collecting system or only part of it.

The renal cortex typically has an echotexture that is quite similar to that of the liver. However, the presence of renal cysts always indicates renal dysplasia. Increased renal parenchymal echogenicity is less specific but may also be an indication of dysplasia.

Finally, it may be important to determine the fetal sex. Posterior urethra valves are a relatively common urinary tract abnormality and are seen only in male infants. In females, bladder outlet obstruction is caused only by prolapsing ureterocele, which is very unusual. Renal anomalies may be associated with other structural anomalies as part of a syndrome or as part of conditions such as the VACTERL syndrome, in which abnormalities involve the vertebra, the rectum, the heart, the esophagus, and the limbs.

SPECIFIC URINARY TRACT ABNORMALITIES DIAGNOSED PRENATALLY

Bilateral Renal Agenesis

Bilateral renal agenesis is estimated to occur in approx 1 in 4000 births. In some cases, bilateral renal agenesis has a possible X-linked autosomal-recessive or autosomal-dominance type of inheritance. Lack of renal function and poor urine output result in associated pulmonary hypoplasia, and the condition is universally fatal. This is described as Potter's syndrome.

Unilateral Renal Agenesis

The incidence of unilateral renal agenesis is not known, but it is believed to be 4 to 20 times more common than bilateral renal agenesis. In a minority of cases, a family history may be present. The diagnosis is difficult to make. Fetal position commonly precludes ideal visualization of the renal fossa. Clearly, the possibility of an absent kidney diagnosed prenatally warrants postnatal evaluation by ultrasound.

Hydronephrosis

Hydronephrosis is the most common fetal urinary tract abnormality seen with prenatal ultrasound and refers to dilatation of the upper uri-

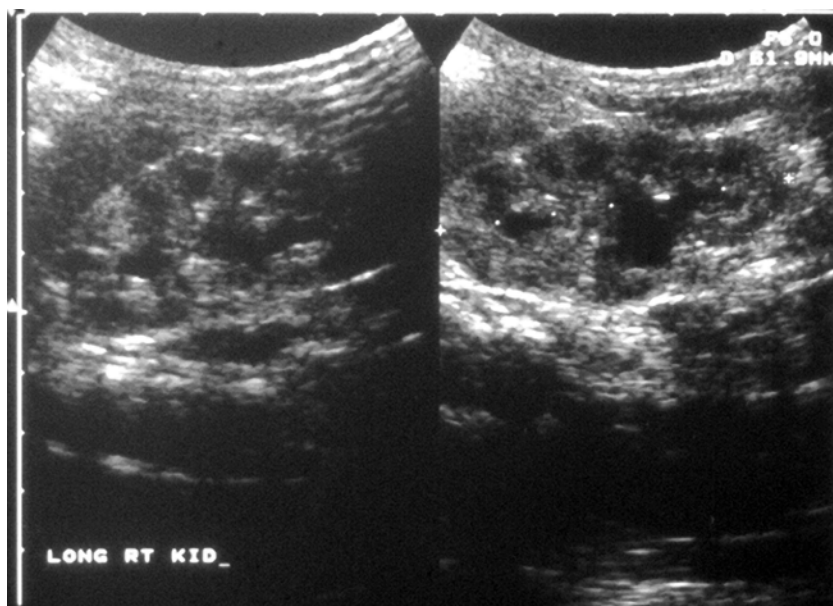


Fig. 1. Bilateral dilatation of the renal pelvic with mild dilatation of the calyces. Note normal echogenicity of the cortex with distinct corticomedullary junction (the medulla appears less echogenic than the cortex because of higher water content in the renal collecting tubules).

nary tract (Fig. 1). It should be emphasized that dilatation is not always associated with obstruction of the urinary tract.

Minimal dilatation of the renal pelvis is a very common finding on prenatal ultrasound and has been diagnosed with increasing frequency as ultrasound technology has improved. Because of the risk of permanent renal damage caused by obstruction, it is crucial to make an accurate early diagnosis of the lesion. Mild prenatal renal collecting system dilatation, however, generally resolves without clinical sequelae (8). Frequent rescanning raises healthcare costs and patient anxiety with no recognized benefit to the fetus. The difficulty has been in determining objective criteria to distinguish clinically significant from insignificant urinary tract dilatation.

Grignon et al. (9) proposed using measurements of the anteroposterior (AP) diameter of the renal pelvis and the ratio of the AP diameter of the renal pelvis to the AP diameter of the kidney. A renal pelvis measuring less than 5 mm in the AP diameter is considered normal. A renal pelvis measurement of 6–9 mm and a renal pelvis kidney diameter ratio of less than 50% in the absence of rounded dilatation of the calyces has been reported to increase in size rarely or to require postnatal treatment (9).

Dilatation of the renal pelvis more than 10 mm at any gestational age, particularly when the ratio of the renal pelvis diameter and the kidney diameter is greater than 50%, is considered abnormal. Some authors believe that dilatation of the renal calyces is evidence of an abnormal urinary tract dilatation even with minimal dilatation of the renal pelvis. Recommendations have made to follow these fetuses regularly during the rest of the pregnancy. In current guidelines, follow-up prenatal and postnatal scans are recommended for patients who have an AP diameter greater than 4 mm between 15 and 20 wk of gestation, those with AP diameter greater than 8 mm between 20 and 30 wk of gestation, and those with AP diameter greater than 10 mm between 30 wk of gestation and term. One prenatal follow-up renal ultrasound is recommended when the pelvis is moderately dilated because *in utero* progression occurs in as many as 10% of cases. If prenatal dilatation of the renal collecting system has been documented and has been shown to persist, the patient should be evaluated by ultrasound shortly after birth. There is some debate regarding the exact timing of postnatal ultrasound, but in general it should be carried out within 1 wk after delivery to ensure proper follow-up.

UPJ Obstruction

UPJ obstruction represents the most common cause of neonatal dilatation of the upper urinary tract. UPJ obstruction may be caused by a distorted arrangement of the smooth muscle at the level of the ureteropelvic junction or by the presence of fibrous adhesions, kinks, ureteral valves, or abnormal vessels (10). UPJ obstruction is usually unilateral but may be bilateral in as many as 10–15% of cases. When bilateral, involvement is usually asymmetrical, with one system displaying more dilatation.

Unilateral UPJ obstruction may be associated with contralateral MCDK or renal agenesis. If the UPJ obstruction is severe and either of these associations is present, oligohydramnios may be present. When obstruction is unilateral and the contralateral kidney is normal or there is bilateral involvement when the obstruction is not too severe, renal function is generally well preserved, with normal production of amniotic fluid. Increases in the degree of dilatation *in utero* are generally rare, but the degree of dilatation is usually greater than what is observed postnatally. One important aspect is that the degree of dilatation of the renal collecting system does not necessarily correlate with renal function impairment as measured postnatally. UPJ obstruction, even when bilateral, is not likely to be fatal.

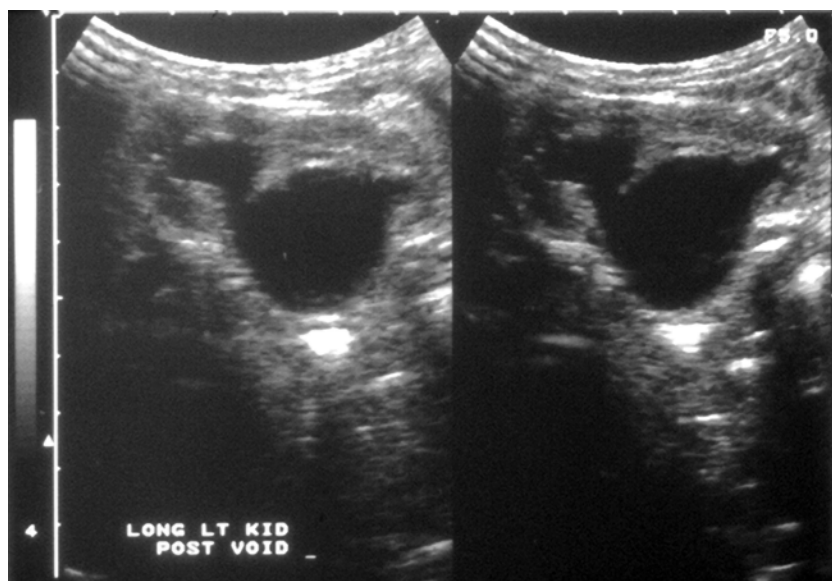


Fig. 2. Ureteropelvic junction obstruction as seen on prenatal ultrasound. Note dilatation of renal pelvis.

The prenatal sonographic diagnosis of UPJ obstruction requires demonstration of a dilated renal pelvis with or without dilatation of the renal calyces and absence of dilatation of the distal ureter (Fig. 2). The bladder should be normal. In some cases, the renal cortex may be significantly thinned. There may be some association with renal dysplasia, depending on the severity and the timing of the obstruction. In the most severe cases, the involved kidney may be reduced to a large unilocular cyst and may actually be shown to have no function when studied postnatally. If the collecting system ruptures, there may be associated urinoma or urinary ascites.

Of concern is that other anomalies of the urinary tract may occur in as many as 25% of cases in association with UPJ obstruction. These should be looked for during postnatal ultrasound evaluation.

UVJ Obstruction and Megaureter

UVJ obstruction is the second most common cause of dilatation of the renal collecting system in the fetus, accounting for as many as 25% of cases. It is usually unilateral. Bilateral dilatation is found in approx 13% of cases. Reported associated anomalies include contralateral renal agenesis, complete or incomplete duplex collecting system, and contralateral cystic dysplastic kidney. The fetal diagnosis of UVJ obstruc-



Fig. 3. Megaureter seen on prenatal ultrasound. The renal pelvis is dilated as is the markedly enlarged ureter, which can be followed down to the bladder.

tion is suggested when there is dilatation of the renal collecting system including the calyces in association with the tortuous fluid-filled tubular structure and in continuity with the renal pelvis closely approximated to the fetal spine (Fig. 3).

Nonobstructive causes of ureteral dilatation may be hard to distinguish from distal ureteral obstruction at the level of the bladder. Fetuses with vesicoureteral reflux, bladder dysfunction, and nonrefluxing, nonobstructive megaureter may have a dilated ureter and dilatation of the renal collecting system. As with UPJ obstruction, if the remainder of the urinary tract is normal, fetal urine production and amniotic fluid level should be normal, and the prognosis is generally excellent. The definitive differentiation of UVJ obstruction from other nonobstructive causes of megaureter usually cannot be made until the postnatal period.

Duplicated Collecting System

In fetal hydronephrosis, particularly when the ureter is dilated, an attempt should be made to determine whether the dilatation involves the entire collecting system or whether only a portion of the kidney is involved. If excess fluid is demonstrated as a dilated area within the kidney, either in the lower or upper pole of the kidney, a duplicated collecting system should be strongly suspected. Postnatal evaluation is

clearly needed in these cases, including ultrasound and voiding cystourethrogram (VCUG).

Bladder Outlet Obstruction

Bladder outlet obstruction is most commonly the result of posterior urethral valves in a male fetus. This will cause an enlarged fetal urinary bladder, with possible dilatation of the upper urinary tract and some dilatation of the proximal urethra. The most common sonographic finding in fetal urethral obstruction is a dilated or thick-walled (or both) urinary bladder. This is a reliable feature of bladder outlet obstruction. As mentioned, the fetal sex should be determined because bladder outlet obstruction usually occurs in males.

In addition to the presence of a persistently dilated or thick-walled urinary bladder with a dilated posterior urethra, other features of urinary tract obstruction are also helpful in making the diagnosis of bladder outlet obstruction. These include oligohydramnios, pelvicaliectasis, dilatation of the ureter, and possible presence of urinary ascites or a urinoma (Fig. 4).

Dilatation of the upper urinary tract is supportive evidence for urethral obstruction; however, lack of dilatation of the upper urinary tract or oligohydramnios should not preclude the diagnosis of urethral obstruction. Lack of dilatation of the upper urinary tract may also be related to decreased urinary production resulting from renal dysplasia caused by abnormal development of the renal parenchyma. The prognosis for fetal urethral obstruction is quite variable. Poor prognostic indicators include decreased amniotic fluid; absence of dilated upper renal collecting system; and echogenic, small kidneys. In patients with a normal amount of amniotic fluid, survival is generally good.

Multicystic Dysplastic Kidney

MCDK disease is a subset of renal dysplasia thought to result from an early obstruction of the ureter causing maldevelopment of the kidney. In general, this results in formation of renal cysts that arise from the dilated collecting tubule. The cysts may vary in appearance but involve the entire kidney. An MCDK generally has no functioning parenchyma, but occasionally there is a small amount of residual function in areas of preserved renal parenchyma. The classic ultrasound appearance of an MCDK is a paraspinous renal fossa mass composed of multiple noncommunicating cysts of various sizes. The ureter is never visualized, and the renal pelvis is visualized only rarely. The normal reniform contour the kidney is lost. The appearance of the MCDK may change during pregnancy.

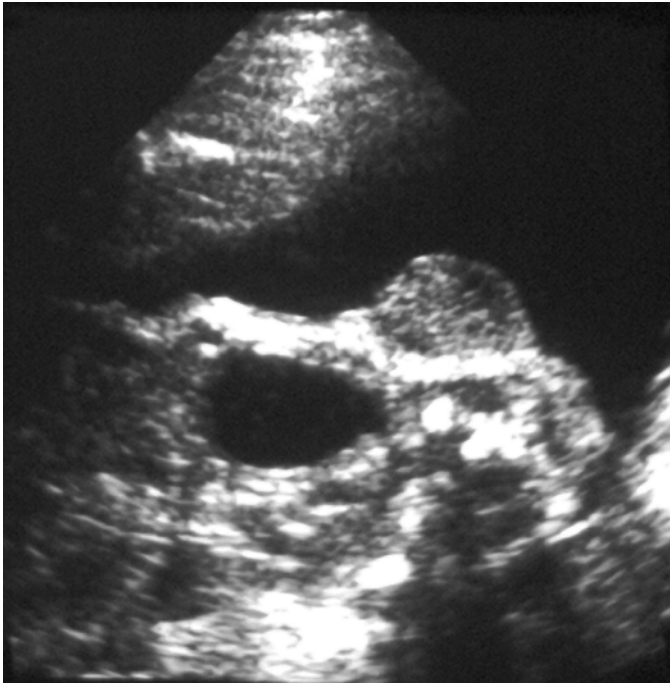


Fig. 4. Prenatal ultrasonographic appearance of the bladder posterior urethral valve. The bladder is large and its wall is thick. The proximal urethra appears enlarged.

When MCDK is identified in the fetus, the prognosis depends on the status of the contralateral kidney. In most cases, MCDK is a unilateral process. However, a significant number of patients (up to 40%) may have other urologic abnormalities that require further evaluation after birth. MCDK is recorded as a sporadic malformation, although a 3–5% familial recurrence rate has been suggested. MCDK also may occur in association with anomalies of the cardiovascular system, central nervous system, diaphragmatic hernia, cleft palate, duodenal stenosis, imperforate anus, and tracheoesophageal fistula.

Further evaluation of the fetus may include prenatal magnetic resonance imaging (MRI), which may help to better define the anatomy of the fetus. However, this technology is still in its experimental stages and warrants further clinical studies to justify its use. The effects of MRI on early fetal development have not been clearly determined.

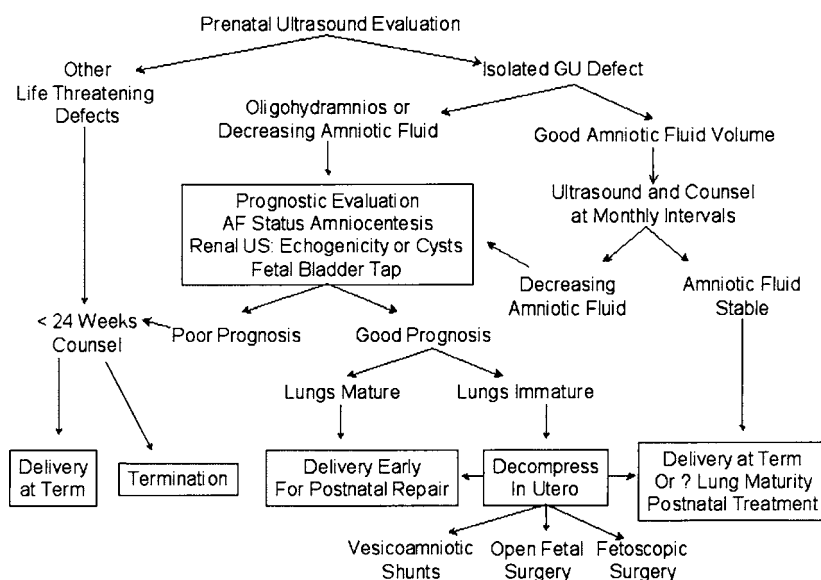


Fig. 5. Algorithm for the prenatal management of fetal hydronephrosis (adapted from ref. 11).

Prognostic Evaluation of the Fetus with Hydronephrosis

A major problem in managing the treatment of prenatal hydronephrosis is determining which fetuses with bilateral hydronephrosis might be candidates for intervention. Determining which obstructions are severe enough to compromise renal and pulmonary development of the fetus but are not so severe as to cause renal failure at birth is a difficult process. Several methods have been suggested to assess the functional capacity of fetal kidneys, including sonographic appearance of the kidney, volume of amniotic fluid, and measurement of various fetal urine electrolytes and proteins. However, the use of serum biochemistry measures is experimental and requires further validation. Studies are ongoing both in Europe and the United States. Fetal intervention is also an experimental procedure and should be carried out only in centers that specialize in that type of approach. Parents should be counseled and referred to these centers only in the early stages of pregnancy. In addition to the risk of injury to both the mother and the fetus with prenatal intervention, there is also concern about the efficacy of prenatal decom-

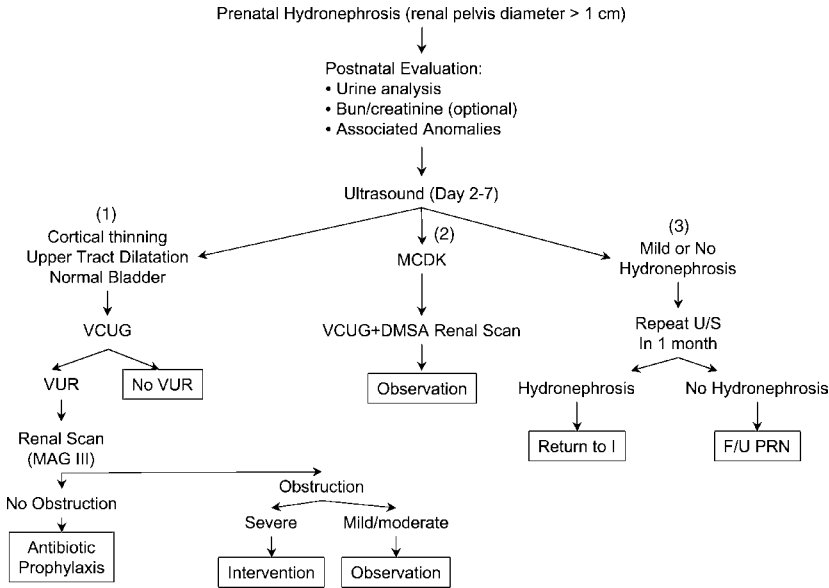


Fig. 6. Algorithm for the postnatal management of fetal hydronephrosis (adapted from ref. 11).

pression of an obstructed urinary tract. Compounding this is the diagnostic uncertainty associated with prenatal ultrasound evaluation of the fetus. Currently, referral to either a pediatric urologist or a fetal treatment center is recommended when fetal oligohydramnios and dilatation of the upper urinary tract is diagnosed. Parents should receive prompt and comprehensive counseling to help them cope with the diagnosis and make decisions regarding management of the fetus. Options include early percutaneous drainage procedures (currently experimental and considered high risk), observation, early delivery, or termination if the condition is considered incompatible with survival (Fig. 5) (11).

POSTNATAL EVALUATION OF THE FETUS DIAGNOSED WITH HYDRONEPHROSIS (FIG. 6)

Fetuses with normal amniotic volume and no other abnormalities noted before 30 wk of gestation should have one ultrasound evaluation prior to delivery to determine progression or regression of hydronephrosis. After birth, ultrasound evaluation should be obtained between the third and seventh day of life because, or in the first 24 h of life, the degree of dilatation of the upper urinary tract may be affected by neonatal fluid shifts (12).

Further postnatal evaluation should include a VCUG to rule out vesicoureteral reflux. In addition, a nuclear renal scan of the kidneys should be carried out to determine residual renal function approx 1 mo after birth. The radionuclide of choice is MAG III, which is bound to the tubular cells and then excreted in the urine. The incidence of urinary tract infection in children with dilatation of the upper urinary tract is estimated at approx 10%. Prophylactic treatment with a penicillin-derivative antibiotic is recommended to prevent urinary tract infection. Circumcision may be indicated in males to reduce the risk of urinary tract infection.

Parental counseling is important in the management of fetuses diagnosed with urologic abnormalities. Clearly, the news of an abnormality noted on a prenatal ultrasound will cause significant fear and anxiety for the parents. Careful counseling and mapping out of the management of the fetus is paramount. Consultation with specialists such as obstetricians who treat high-risk pregnancies, pediatric urology specialists, and radiologists with help alleviate some of these fears and provide guidance about further management of the child.

THE FUTURE

Whereas the last two decades have seen significant advances in the understanding of the natural history of prenatal diagnosed hydronephrosis, the development of selection criteria for *in utero* intervention has not resulted in significant changes in the management of these children. Rather these advances have allowed early identification of potential urologic lesions, which are in general managed postnatally by providing early confirmation using ultrasound screening and further evaluation by radionuclide scanning of the kidneys and bladder evaluation by VCUG. Clearly the most important issue for primary care physicians is to ensure appropriate follow-up and referral to a pediatric urologic specialist to ensure that the child is managed in a timely manner and treated appropriately.

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2

Pediatric Urologic Emergencies

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INTRODUCTION

Fortunately, few emergencies in pediatric urology result in loss of life. However, these true emergencies, if not recognized and treated quickly, can lead to loss of or severe injury to the affected organ (testicular torsion and severe renal trauma) or to possible loss of life (adrenal hemorrhage and urosepsis). Table 1 lists the emergencies that a urologist may be called on to evaluate and treat. In addition, there are a number of urologic conditions that require expeditious evaluation and treatment. These conditions are referred to as “urgencies” and are listed in Table 2. Although many of these conditions are not immediate threats to life or to end organs, failure to properly diagnose and treat them can have catastrophic consequences.

PEDIATRIC EMERGENCIES

Abdominal Masses

HYDRONEPHROSIS

Most abdominal masses in children are found in the retroperitoneum or genitourinary tract and should, therefore, be evaluated by a pediatric urologist (1,2) (Table 3). The most common abdominal mass in the

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Table 1
Pediatric Emergencies

Acute scrotum
Ambiguous genitalia
Renal vein thrombosis
Renal artery thrombosis
Adrenal hemorrhage
Posterior urethral valves
Priapism
Trauma
Child abuse
Abdominal mass
Urolithiasis
Paraphimosis

Table 2
Pediatric “Urgencies”

Exstrophy
Prune-belly syndrome
Hematuria
Imperforate anus
Urethral prolapse
Urinary tract infections
Myelodysplasia

newborn remains hydronephrosis (3,4) (Fig. 1 A,B), particularly as a result of ureteropelvic junction (UPJ) obstruction (5,6) (Fig. 2). In most cases, the diagnosis is made by prenatal ultrasonography. In most fetuses, hydronephrosis is unilateral and should be followed by a pediatric urologist until birth (7). The newborn should be placed on antibiotic prophylaxis and sonography should be performed. Beware the ultrasound done within the first 24 to 72 h postdelivery because the relative dehydration that occurs during the birth process may mask true hydronephrosis (8). The ultrasound should be repeated 1 wk to 1 mo after birth to confirm prenatal findings. A voiding cystourethrogram (VCUG) is performed to look for vesicoureteral reflux (VUR), and a well-tempered renogram is done to evaluate for obstruction (9,10). If obstruction or reflux is not found, the patient can be taken off antibiotic prophylaxis. Treatment for a confirmed UPJ obstruction should be based on the degree of obstruction and whether the obstruction is unilateral or bilateral (7,11). Clearly, severe bilateral obstruction, as demonstrated on ultrasound and furosemide renal scan, must be corrected

Table 3
Abdominal Masses
in Neonates and Children

- Hydronephrosis
 - MCDK
 - Polycystic kidney
 - Distended bladder
 - Hydrometrocolpos
 - Ovarian cyst
 - Neuroblastoma
 - Wilms' tumor
 - Mesoblastic nephroma
 - Adrenal hemorrhage
 - Renal vessel thrombosis
 - Pyloric stenosis
 - Germ cell tumors
 - Hepatic lesions
 - Sacroccocygeal teratoma
- MCDK, multicystic dysplastic kidney



Fig. 1. (A) Hydronephrotic right kidney in a newborn.

early (12). Many children who have unilateral UPJ obstruction with function greater than 40% in the ipsilateral kidney can be followed with ultrasound and renal scintigraphy (13). Ransley et al., Koff and

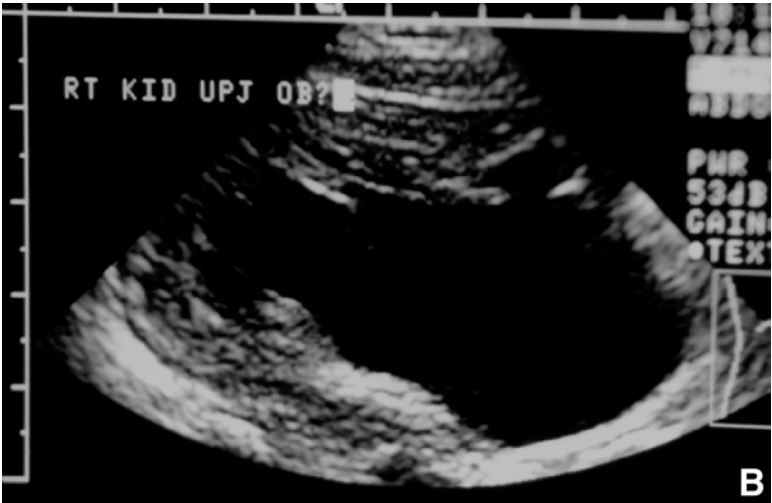


Fig. 1. (B) Marked right hydronephrosis in another child with prenatal diagnosis of hydronephrosis. There is marked pelviectasis and caliectasis.

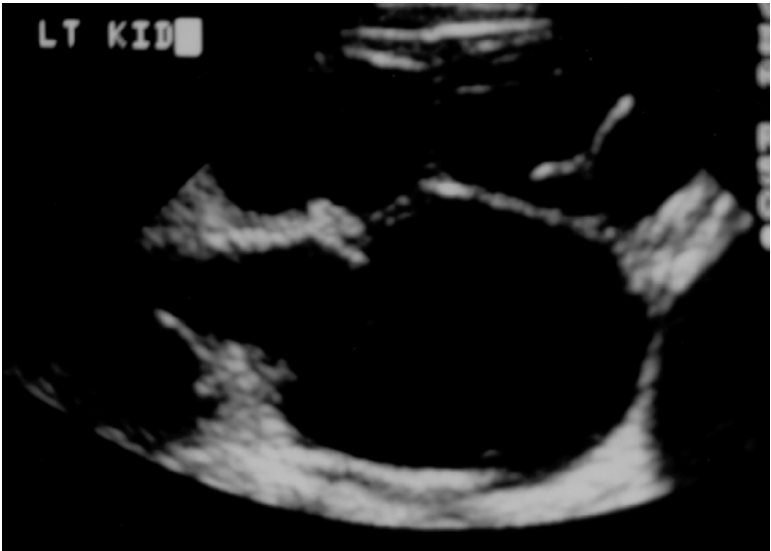


Fig. 2. Severely hydronephrotic left kidney, with thin parenchyma. At the bottom right of the ultrasound is the bladder.

Campbell, and others have demonstrated that careful follow-up of children with stable hydronephrosis and obstruction is safe. In most children, the obstruction resolves spontaneously (13–17).

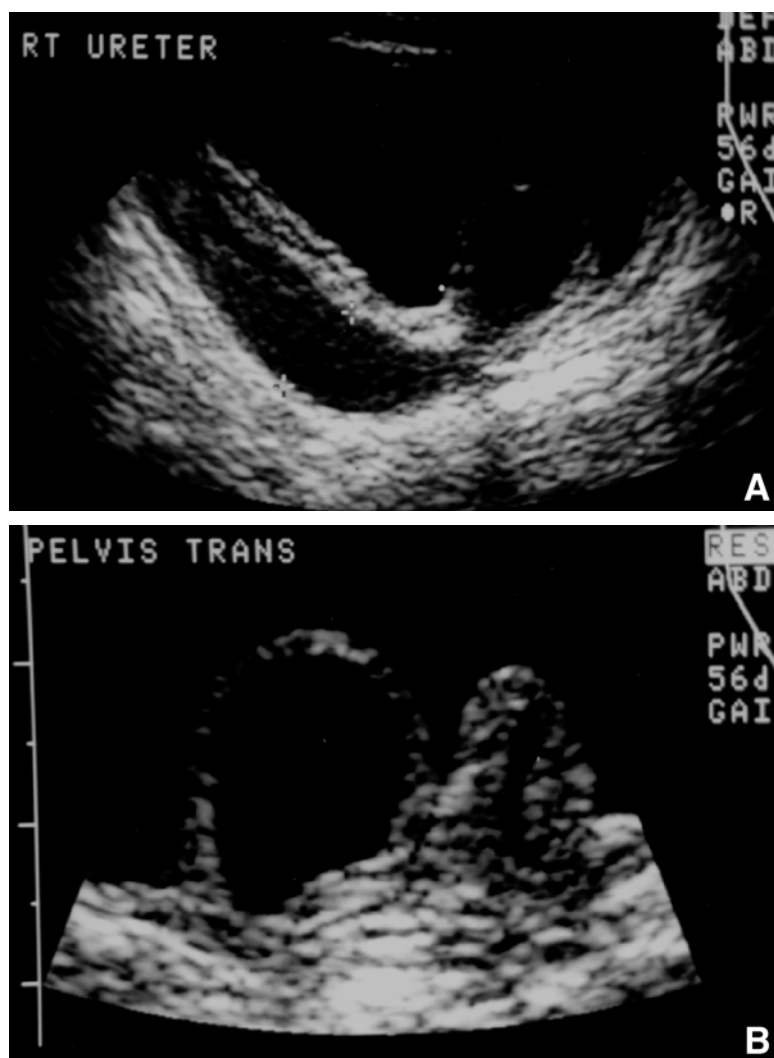


Fig. 3. (A) Right hydroureter entering the bladder and ending into an ureterocele. (B) Bilateral single-system ureteroceles.

In addition, hydronephrosis may be the result of obstruction at the ureterovesical junction by ureteroceles (Fig. 3 A,B). In fact, an ectopic ureterocele is the most common cause of bladder outlet obstruction in females (10% of cases) (18) and the second most common cause in males (second to posterior urethral valves) (19,20). These patients also have hydroureter down to the level of the bladder, and classic ultrasound



Fig. 4. Large introital mass, which was a prolapsed ureterocele in a female.

finding of an echogenic rim of tissue that may protrude into the bladder neck (21). Prolapse of the ureterocele may develop in some patients (Fig. 4), and older patients may have calculi within the ureterocele resulting from urinary stasis. Evaluation includes renal and bladder ultrasound, VCUG, and if indicated, a furosemide renal scan. Treatment for obstructing ureteroceles is somewhat controversial. Some authors advocate transurethral incision (22–24). However, there is a high incidence of VUR as a consequence of incision, possibly necessitating re-implant and bladder floor reconstruction (25). Resection with ureteral re-implant and reconstruction of the bladder floor has also been recommended. Obstructing ureteroceles associated with complete ureteral duplication are more common and need to be evaluated in a similar manner to single systems (26). The upper pole moiety is almost always affected and may have minimal function. Consideration should be given to performing a heminephroureterectomy in children with obstructed upper pole moieties and poor function. Many children with complete duplication and an upper pole ureterocele also have reflux into the lower pole moiety and should be followed over time (18).

Other lesions that may be misinterpreted as hydronephrosis include multicystic dysplastic kidney (MCDK), cystic nephroma, and autosomal-dominant and autosomal-recessive polycystic kidney disease. MCDK is the second most common abdominal mass found in infants (27). Both sexes are equally affected. Children found to have MCDK should have a VCUG because these patients have a high incidence of

contralateral vesicoureteric reflux (28). The diagnosis can be made by ultrasound, which demonstrates a multiloculated mass with little or no parenchyma. The cysts do not communicate. If there is any question whether the child has MCDK or severe UPJ obstruction, a renal scan will confirm the diagnosis (29). Treatment has changed since the late 1980s. Whereas many children with MCDK underwent nephrectomy in the past, they are now being followed with serial renal ultrasounds. MCDKs generally regress over time. Surgery is reserved for those patients in whom MCDK does not regress or causes symptoms (30,31).

MIDLINE ABDOMINAL MASS

A child with a midline abdominal mass should also be evaluated with ultrasonography. In the emergency department, the most common cause of a midline lower abdominal mass is a distended bladder (32). In males, the presence of posterior urethral valves must be considered and evaluation undertaken to confirm or refute the diagnosis (33). In addition, neurologic causes of urinary retention need to be addressed, such as spinal dysraphism or spinal cord tumor (34).

Hydrocolpos is distension of the vagina that occurs as a result of a build up of cervical mucus behind an imperforate hymen (most commonly) or as the result of some other vaginal abnormality (35). In 1984, Han-Pedersen et al. demonstrated that cervical mucus secretion was a result of maternal estrogen (36). Most neonates will have a lower midline abdominal mass, a bulging mass in the perineum, and hydronephrosis resulting from bladder outlet obstruction caused by the distended vagina. An incision in the hymen is usually all that is needed to completely drain the vagina and relieve the bladder obstruction (35).

Other causes of abdominal mass include ovarian cysts, sacrococcygeal teratomas, and neonatal ascites. Ovarian cysts can be the result of ovarian torsion followed by cystic degeneration of the ovary. More commonly, ovarian cysts are the result of maternal hormonal stimulation and regress quickly in the absence of any stimulus (37). Sacrococcygeal teratoma occurs in 1 in 40,000 births and occurs predominantly in females (38). Like hydrocolpos, sacrococcygeal teratomas can cause outlet obstruction and hydronephrosis (39). Excision of the teratoma can lead to neurogenic bladder (in up to 12% of patients); therefore, the child must be followed to assess for any neurologic sequelae (40).

Urinary ascites can be diagnosed in the fetus or in the newborn period. Ascites is commonly caused by urinary extravasation resulting from urinary tract obstruction or trauma (41). Sahdev et al., in 1997, reported that extravasation of urine occurred most commonly as a result of forniceal rupture in the kidney (42). Some authors believe that extrava-



Fig. 5. Young female with large abdominal mass. Evaluation revealed a large renal mass, which was found to be Wilms' tumor.

sation of urine is a protective mechanism, decreasing the amount of damage to the kidneys from obstruction (43,44). Bladder perforation as a result of umbilical artery catheterization can also lead to urinary ascites (45). The diagnosis can be made by ultrasonography and VCUG in most cases, and the bladder should be surgically repaired (46).

SOLID ABDOMINAL MASSES

Solid abdominal masses are now being diagnosed with increasing frequency in the prenatal period. However, many solid abdominal masses are still discovered by physical examination after birth (Fig. 5). The most common solid abdominal mass in children is neuroblastoma (47). Neuroblastoma is a firm, fixed mass that can cross the midline. It can arise from the adrenal gland or from anywhere along the sympathetic ganglia. Although these lesions can be diagnosed with ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) are usually used to confirm the diagnosis. On KUB, these lesions can have fine calcifications, which suggest the diagnosis. In addition, this tumor is of neural crest origin, and therefore laboratory testing for increased levels of catecholamines (vanillylmandelic acid and homovanillic acid) in the urine is an essential part of the diagnosis of neuroblastoma. Bone marrow biopsy and lymph node sampling are done at the time of surgery because of the very high (90%) incidence of metastatic disease. Patients receive chemotherapy with or without radiation therapy based on the stage of disease (48).

Congenital mesoblastic nephroma is the most common solid mass of the kidney in children less than 6 mo of age. The majority of these masses are discovered during routine well-baby examinations within the first month of life. Although locally invasive, these fibroid-appearing tumors rarely metastasize. Treatment is elective nephrectomy (49).

The most common solid renal tumor in children is Wilms' tumor (50). These children also have an abdominal mass. On CT or MRI, these tumors involve the kidney and are expansile in nature. They rarely cross the midline. A genetic mutation on chromosomes 11p13 and 11p15 has been demonstrated in children with Wilms' tumor. These children may also have hemihypertrophy and aniridia. The pathologic findings may be favorable or unfavorable and will dictate, along with surgical stage, the most appropriate course of therapy. Other solid abdominal masses in children include multilocular cystic nephroma, renal cell carcinoma, pheochromocytoma, adrenal adenoma, adrenal carcinoma, and rhabdomyosarcoma (50,51).

Thrombosis of Renal Vessels

Renal vein thrombosis in neonates is characterized by gross hematuria, abdominal mass, dehydration, or thrombocytopenia (52,53). Renal vein thrombosis is a common cause of gross hematuria in the first month of life. In addition, renal vein thrombosis can be found in children with gross hematuria (54). Low renal artery and venous flow rates appear to predispose children to renal vein thrombosis. Factors that are most commonly associated with renal vein thrombosis include sepsis, dehydration, maternal diabetes, polycythemia, birth asphyxia, and umbilical artery catheterization (55).

Evaluation of children with renal vein thrombosis includes an ultrasound, which demonstrates echogenic streaks and the absence of hydronephrosis. A clot may be seen within the renal vein and may extend to the vena cava. Unilateral renal vein thrombosis is treated with supportive care, namely fluids and correction of any metabolic abnormality. The use of systemic anticoagulation or thrombolytic therapy is usually reserved for children with bilateral renal involvement (56,57). The prognosis for patients with renal vein thrombosis worsens in those with bilateral disease. Children with bilateral renal vein involvement have a higher rate of renal failure. These children require long-term follow-up to manage their renal insufficiency or to identify new-onset hypertension.

The increasing use of umbilical artery catheterization has resulted in an increased incidence of renal artery thrombosis (58). Children with renal artery thrombosis do not typically have an abdominal mass. How-

ever, they may have hematuria, hypertension, and congestive heart failure. The diagnosis can be made and confirmed with Doppler ultrasound, which demonstrates no flow to the affected kidney. Treatment is usually supportive but can include intra-arterial thrombolytic therapy or unilateral nephrectomy (59,60).

Adrenal Hemorrhage

Adrenal hemorrhage is most commonly found in newborns who have been through a dramatic or difficult labor, or who have hypoxia, septicemia, or coagulopathy. The right adrenal gland appears to be the most commonly affected, and 10% of adrenal hemorrhages occur bilaterally (20). Felc in 1995 was able to show an incidence of 1.9 per 1000 births (61). The large and hypervascular adrenal glands in neonates appear to be predisposed to bleeding, especially in those neonates described above. Children may have hemodynamic instability and may also have an abdominal mass.

The diagnosis can usually be made by ultrasound but may be difficult to differentiate from neonatal neuroblastoma. Additional radiographic studies using CT and MRI, and measures of urinary vanillylmandelic acid and homovanillic acid help to solidify either diagnosis. Adrenal insufficiency is uncommon. Treatment is generally supportive, and occasionally transfusion and phototherapy may be used (62).

Posterior Urethral Valves

Posterior urethral valves were originally described by Young et al. in 1919 (63). They described three types of posterior urethral valves. Type I and type III valves were confirmed over time. Type II valves do not appear to exist. Posterior urethral valves are most commonly diagnosed perinatally but can be diagnosed into adulthood (64). Prenatal ultrasound demonstrates a distended, thick-walled bladder, unilateral or bilateral hydronephrosis, and even oligohydramnios in some cases (65). In the nursery, the pediatric urologist may be called to see the newborn who fails to void within the first 24 h of life. On physical examination, a palpable bladder may be found (33). An abnormal urinary stream is found in some neonates. Ultrasound may show unilateral or bilateral hydronephrosis, a thickened bladder wall, and dilation of the posterior urethra. VCUg further identifies the posterior urethral valves and the presence or absence of reflux (66). Some of these children may also have urinary ascites as a result of forniceal rupture caused by bladder outlet obstruction (41,42). The vesicoureteral reflex dysplasia (VURD) syndrome was identified by Rottenberg et al. in 1988 (67). These boys were found to have severe VUR with ipsilateral renal dysplasia. The con-

tralateral kidney did not have reflux. The authors postulated that the severe reflux with dysplasia actually acted as a protective mechanism for the nonrefluxing kidney, and in these boys, renal function after valve ablation surgery was generally normal. Children who are thought to have posterior urethral valves should be placed on antibiotic prophylaxis. The mainstay of surgical therapy for posterior urethral valves is transurethral ablation of the valve leaflets.

This is most commonly performed in a retrograde manner and can be done with electrocautery or laser ablation (68). Antegrade valve ablation has also been described (69). It is important to identify rupture (ablation) of both valve leaflets to assure opening of the posterior urethra. In children whose urethral caliber is too small to accommodate the resectoscope equipment, vesicostomy is a viable alternative. The long-term prognosis depends on several factors, including renal function, before and after valve ablation, and the long-term management of bladder function. Children with serum creatinine level less than 0.7 mg/dL after valve ablation surgery have a better prognosis (68). The valve-bladder syndrome has been described and can lead to dysfunction of the bladder and long-term upper track dilation (70,71). Some form of renal failure develops in many of these children at the time of puberty because of increased muscular mass along with voiding dysfunction.

Therefore, it is crucial for the pediatric urologist to maintain long-term follow-up on all boys with posterior urethral valves.

Ambiguous Genitalia (Intersex Disorders)

Intersex disorders are now being identified in the antenatal period. Ultrasound techniques, amniocentesis, and chorionic villae sampling in the prenatal period have assisted in the antenatal diagnosis of intersex disorders (72,73). However, the presence of ambiguous genitalia continues to be the most common means of identifying a child with an intersex disorder (Fig. 6 A,B). The most common cause of ambiguous genitalia is congenital adrenal hyperplasia (74) and 21-hydroxylase deficiency is the leading cause of congenital adrenal hyperplasia. This results in the inability to synthesize cortisol, leading to overproduction of androstenedione as a result of overstimulation of the adrenal gland by the pituitary gland and hypothalamus. Androstenedione is then metabolized to testosterone and dihydrotestosterone, resulting in virilization in females (75). In addition, the lack of mineralocorticoid and glucocorticoid can lead to elevated serum potassium level and decreased serum sodium level, resulting in dehydration or cardiac dysrhythmia (76). Therefore, it is essential that children with any form of ambiguous genitalia have serum chemistry testing to rule out electrolyte abnormalities.

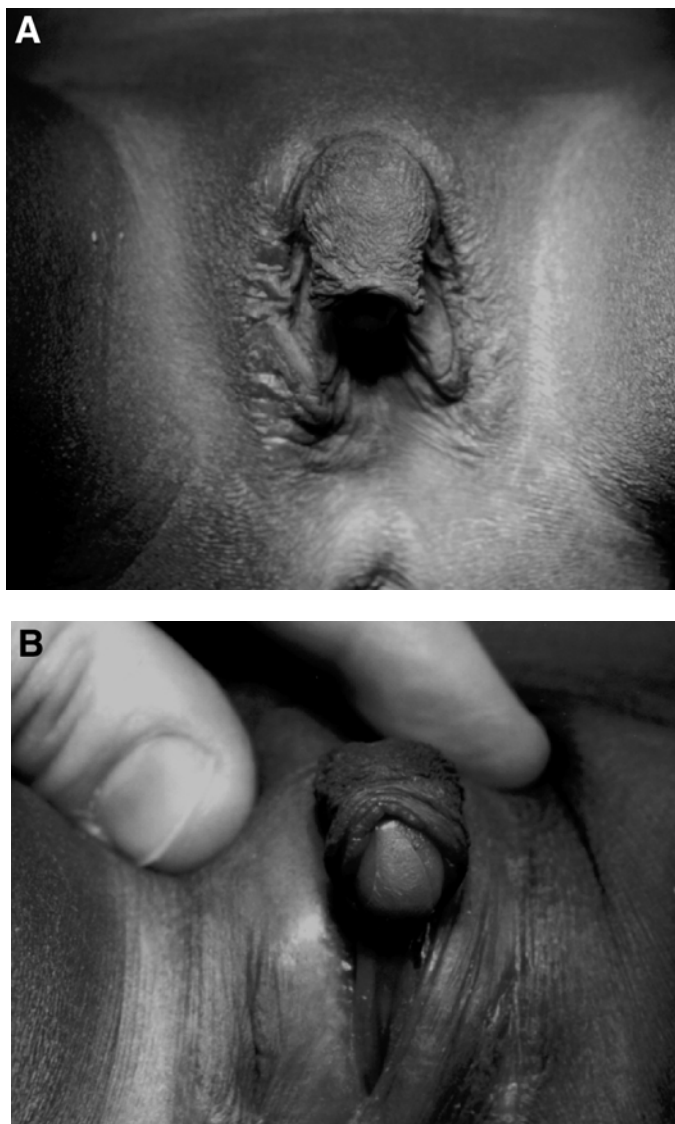


Fig. 6. (A) Toddler with ambiguous genitalia. Note the absence of gonads in the labioscrotal folds. (B) Same child with retraction of phallus. Child was found to have congenital adrenal hyperplasia resulting from to 21-hydroxylase deficiency.

These children should also have a karyotype analysis performed. The family history may include prior neonatal deaths, sterility or amenorrhea, and maternal medication use during pregnancy. In addition to



Fig. 7. Child from Fig. 6 after feminizing genitoplasty.

family history, thorough physical examination and laboratory studies should be performed. These studies, along with the karyotype analysis, will diagnose the majority of children with intersex disorder (77). In addition to potentially life-threatening electrolyte abnormalities, these children are also considered to have a social emergency. It is difficult for parents to understand that the correct sex of rearing cannot be determined at the time of birth. It will be based on the karyotype; phenotype; levels of 17-hydroxyprogesterone, testosterone, and dihydrotestosterone; ultrasound of the pelvis (looking for the presence of female organs); and genitography of the child. Understandably, parents can sometimes be impatient waiting for test results. Therefore, treatment of the child with an intersex disorder must be individualized and should include specialists from other fields. Once gender assignment has taken place, surgical reconstruction can be quite successful (Fig. 7).

Child Abuse

Child abuse is defined by the National Center for Child Abuse and Neglect as “any contact or interaction between a child and an elder where the child is used for sexual stimulation of that individual or another” (78). Perineal examination of both boys and girls should be routinely performed in the physician’s office. Examination of the vagina may reveal an enlarged hymenal opening. However, Gardner (79) has

described normal hymenal diameter and appearance of the introitis. Most institutions have a mechanism for using a multidisciplinary approach to evaluate any child suspected of being a victim of abuse. For any child seen in the emergency department with what appears to be a sexually transmitted disease, it is important not only to diagnose and treat the infection correctly, but it is also important to ascertain how the disease was acquired. In the prepubertal child, any evidence of sexually transmitted disease must be considered child abuse until evaluated and proven otherwise (78,80). In addition, pregnancy may be the first sign of child abuse. In boys, examination of both the back and perianal region is important in looking for signs of abuse. It is essential to evaluate children for possible sexual abuse in any suspected case.

Trauma

Most genitourinary trauma occurs as a result of blunt injury. The kidney is the most common genitourinary structure injured as a result of trauma. Injuries range from contusions to severe pedicle injuries. A proportionally increased kidney size, paucity of perirenal fat, and persistence of fetal lobulation are all factors that predispose the kidney to injury (81). The presence of renal anomalies is also a predisposing factor to renal injury in up to 25% of cases (82). The kidney is injured most often in deceleration injuries, such as a fall, a motor vehicle accident, or a sports injury (83). Hematuria and flank tenderness are the most common findings associated with renal injury. However, as is seen in the adult population, the degree of hematuria does not necessarily correlate with the severity of the renal injury. In most emergency departments, evaluation of the child with trauma and any degree of hematuria is done with CT to assess the genitourinary tract (84). If renal trauma is found, the treatment is usually conservative, with admission to the hospital for more severe renal injuries (parenchymal lacerations and shattered kidney). As in adults, surgical treatment is reserved for the hemodynamically unstable patient or for instances when there are other associated abdominal injuries that require surgical intervention (85). The ureter is an infrequently injured structure (86). However, disruption can occur at the UPJ in a child who has undergone blunt abdominal trauma and had an unidentified UPJ obstruction (81–84). The bladder is more vulnerable to trauma as a result of its relative intra-abdominal location. Most trauma injuries are associated with pelvic fractures and most are extraperitoneal in location. Surgical exploration is recommended for children with bladder rupture when there is intraperitoneal rupture or associated bony fragments (87).

Urethral injuries occur most commonly at the prostatomembranous junction. These occur as a result of rapid deceleration injuries, as seen in children and adults with pelvic fracture. The urethra may also be injured by a straddle injury, as occurs in boys who fall onto the crossbar of a bicycle (88). The penis can be injured by various mechanisms. In toddlers and young boys, injury to the penis as a result of being crushed between the toilet seat and the commode is a common mechanism of injury. Zipper injuries of the penis and foreskin also occur and can be extremely difficult to treat in the apprehensive child (32). Flowerdew et al. in 1977 described a successful technique to disassemble the zipper in this type of injury (89). Strangulation or tourniquet injuries may also occur as a result of human hair or string being wrapped around the penis. Many also occur as a result of rubber bands, wires, or other structures placed around the penis (32). Treatment of this type of injury depends on identification of the offending agent.

Scrotal and testicular injury most often occur as a result of blunt trauma. These injuries range from scrotal ecchymosis to testicular rupture. Many children are injured during sports activities because they are not wearing proper protective gear. A scrotal ultrasound may be needed to assess the integrity of the testicular parenchyma, and scrotal exploration may be required to repair a ruptured testicle (90). Vulvar trauma commonly occurs as a result of a straddle injury, which can be seen when a girl falls onto the bar of a boy's bicycle (88). These injuries can be treated conservatively in the majority of cases but can be of such severity as to require a general anesthetic for proper diagnosis.

Phimosis, Paraphimosis, and Circumcision Injuries

Few newborns have a fully retractable foreskin at birth. Phimosis, or a stenosed prepuce, can be associated with a forceful retracting of the prepuce over the glans penis and the resultant preputial scarring that occurs. The natural history of the adherent foreskin is to eventually loosen and become fully retractable by the age of 10 or 11 yr. Phimosis may be caused by episodes of balanitis, balanoposthitis, and urinary tract infections (35,91). Treatment is commonly circumcision, but a dorsal or ventral slit can correct the problem and allow the child to keep the prepuce (92,93). Paraphimosis results from retraction of the prepuce proximal to the glans for a prolonged period of time. As result, edema develops and causes a progressive constriction around the penis. Light sedation may be required in younger children to reduce the paraphimosis. To reduce the paraphimosis, manual compression of the glands is done while simultaneously reducing the edematous foreskin. The edema resolves rapidly after reduction of the foreskin (94).

Most neonatal circumcisions are performed in the nursery by either pediatric or gynecologic personnel. There are few indications for neonatal circumcision, and most males in the world are not circumcised. The complication rate associated with circumcision is 0.2–10%. The incidence may be even higher because many patients are treated without referral. The most acute complications are bleeding, infection, partial amputation, and necrosis. Necrosis is most commonly caused by overuse of electrocautery, whereas partial amputation may be the result of incorporation of the frenulum into a Mogen clamp (95). Persistent bleeding can be treated by direct pressure, placement of absorbable suture, or cautery. In the event of penile amputation, the amputated portion can be re-attached in the majority of cases. Long-term, nonacute complications include removal of excess skin, skin bridges, skin chordee, epidermal inclusion cysts, and development of a concealed (buried) penis (95). A concealed penis can result from the penis retracting below the circumcision scar and subsequent scar contraction (96).

Acute Scrotum and Scrotal Masses

A child with an acute scrotum is one of the true emergencies for a urologist. The differential diagnoses include torsion of the spermatic cord, torsion of a testicular or epididymal appendage, and epididymitis. Most patients have a history of severe pain, which is usually unilateral and of sudden onset. The patient is generally uncomfortable and has an enlarged, erythematous hemiscrotum on examination. If the pain is prolonged, there may be skin fixation to the underlying testicle (90). The testis generally lies horizontally, and in many cases, cremasteric reflex will be absent. In addition, pain is severe over the testis and spermatic cord. Many authors suggest surgical exploration for any child with suspected torsion. However, many emergency departments perform color Doppler imaging to assist in the diagnosis. Testicular scintigraphy can also be performed but has been replaced in many institutions by color Doppler ultrasound (97). One must be cognizant of the potential delay in diagnosis by performing ultrasonography or scintigraphy; therefore, surgical exploration is indicated for any patient whose history and physical examination are consistent with testicular torsion. At the time of surgery (Fig. 8 A,B) the testis is detorted and wrapped in a warm, moist sponge to allow for revascularization of the gonad. During this time, the contralateral testis should undergo orchiopexy because the incidence of asynchronous torsion may be as high as 50% (98). On completion of the contralateral orchiopexy, the ipsilateral torsed testis should be examined for viability.

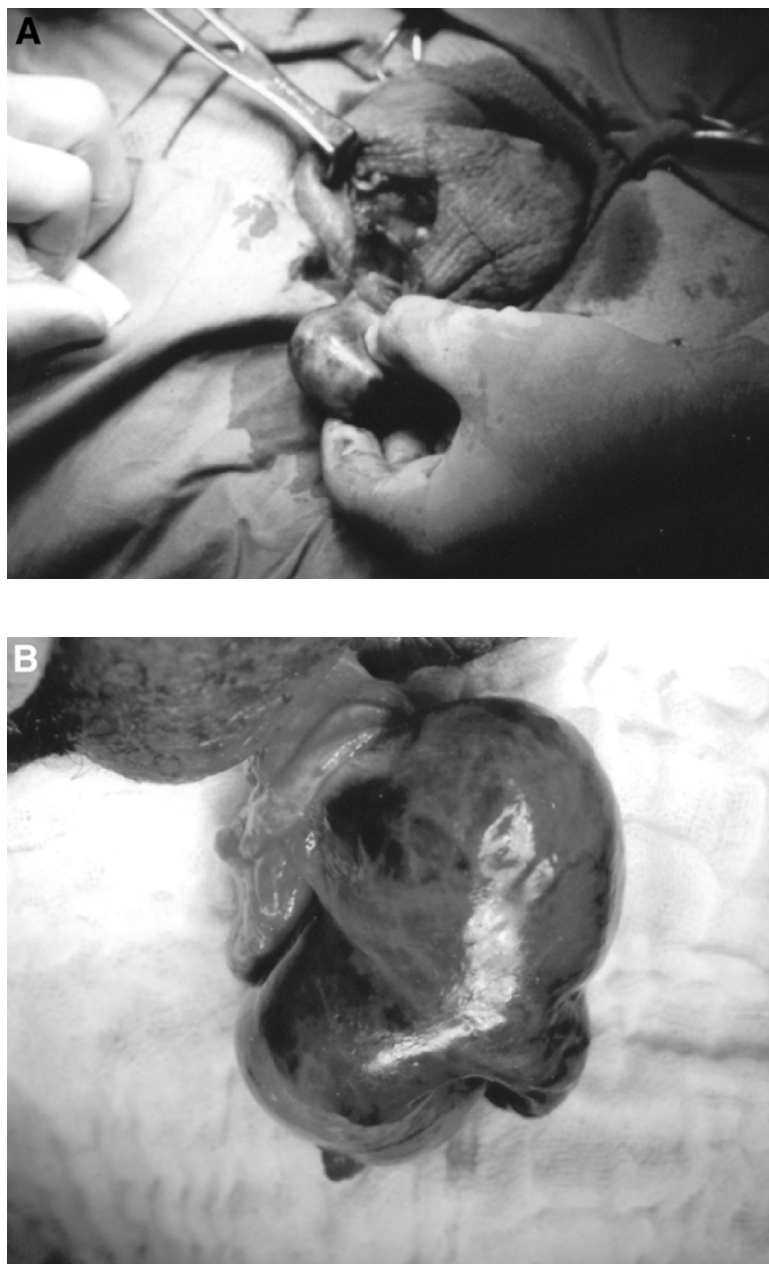


Fig. 8 (A) Exploration of patient with severe hemiscrotal pain and physical examination results consistent with torsion. At exploration, a 720° rotation was noted. (B) Same testis after contralateral orchidopexy. The gonad did not demonstrate any flow and was removed.

If it is deemed viable, it is fixed to the scrotal wall. If it is nonviable, it is removed. Torsion of the appendix testis or the appendix epididymis occurs most often in boys around the time of puberty. The signs and symptoms are similar to those of testicular torsion; however, the pain tends to be more focal in location than in testicular torsion (90,97). Dresner described a “blue dot” sign that is considered to be pathognomonic for torsion of the appendix testis (99). The diagnosis can usually be confirmed by patient history, physical examination, and color Doppler sonography. Epididymitis is much less common in pediatric patients than in adults, but it can occur in all age groups. The onset of testicular pain is more gradual than in testicular torsion but can be just as severe. Color Doppler sonography will demonstrate good testicular blood flow, enlargement, and increased flow to the epididymis (100). The cause of epididymitis can be bacterial or inflammatory (as the result of reflux of sterile urine) (101). Treatment includes antibiotics and anti-inflammatory agents, scrotal support, and restriction of strenuous activity.

The list of differential diagnoses of scrotal masses is shown in Table 4. In the neonate, the differential diagnosis is limited and includes torsion, hydrocele, incarcerated hernia, testis tumor, trauma, and lesions resulting from a patent processus vaginalis. Although there is little debate regarding the existence of neonatal testicular torsion, there is controversy regarding the mechanism of torsion, the risk of bilaterality, and the need for exploration and contralateral testis fixation (102). Most cases of neonatal torsion are considered to be extravaginal, involving the testis, epididymis, and tunica vaginalis. The most common findings are a nontender, firm scrotal mass or a nonpalpable testis (in older children) (103). Color Doppler ultrasound can confirm torsion in the former. Meconium, hematoma, and tumor seeding from abdominal or adrenal tumors can be found in the scrotum as a result of a patent processus vaginalis (102,104). Testis tumors are rare but if found, should be explored surgically and resected as indicated. In older children, testicular tumors are rare but need to be considered in the evaluation of scrotal mass (102). Therapy (surgery, chemotherapy, and radiation) is individualized depending on the tumor. There is a role for testis-sparing surgery and for observation only for the more benign tumors (102). Varicoceles occur in up to 15% of adolescents (105). They are most commonly on the left and decompress when the patient is in the supine position. The indication for intervention is testicular growth failure. Treatment includes embolotherapy and surgical vein ligation. Kass demonstrated that when internal spermatic vein ligation was performed in children with testicular growth failure, greater than 75% had “catch-up” growth of the affected testis (106).

Table 4
Scrotal Masses

Neonatal torsion
Hydrocele
Incarcerated hernia
Spermatic cord torsion
Testis tumor
Epididymitis
Paratesticular tumor
Varicocele
Epididymal cyst
Epididymal tumor
Idiopathic edema
Schönlein-Henoch purpura
Cavernous hemangioma
Funiculitis
Patent processus lesions

Priapism

Priapism can occur in all age groups. In most children, a hematologic disorder is the cause of priapism. The most notable cause of priapism in children is sickle cell disease (92). Priapism in this group of children may signal a sickle cell crisis, but more commonly it is an isolated event. This form of priapism is most commonly a low-flow or ischemic condition resulting from decreased venous outflow (107). The patient has a very hard, painful erection with a soft glans and soft corpus spongiosum. Initial treatment of this form of priapism includes oxygen supplementation and intravenous fluid hydration. In addition, analgesia should be provided. Priapism should be treated more aggressively if the erection does not subside. This includes aspiration and irrigation of the corporeal bodies, use of intracorporeal vasodilating agents, hypertransfusion therapy, and surgical treatment. As in adults, prolonged priapism in children may be associated with corporeal fibrosis and erectile dysfunction (108).

Urolithiasis

It is estimated that up to 3% of all urinary calculi occur in children (109). Renal calculus disease in children has a number of causes, including furosemide therapy, glucocorticoid therapy, relative hypophosphatemia, and low birth weight (110). Children with urolithiasis may have gross or microscopic hematuria and pain. Renal stone disease can be treated with observation except in patients who are symptomatic.

Modes of therapy include extracorporeal shock wave lithotripsy, endoscopic stone manipulation, and open surgery (111).

PEDIATRIC URGENCIES

Hematuria

There are many causes of hematuria in children (Table 5) (112). Medical processes occur more frequently than surgical processes in this population. Lesions involving the glomerulus, renal interstitium, renal vascular supply, or urinary tract can all result in hematuria. An accurate diagnosis can be made by obtaining a thorough patient history and by performing a physical examination and urinalysis. One of the more common causes of hematuria is an acute postinfectious glomerulonephritis such as poststreptococcal glomerulonephritis. Children with poststreptococcal glomerulonephritis frequently have a history of illness 1 to 3 wk before the onset of hematuria. The patient may be fully recovered or may have malaise, headache, nausea, and vomiting. Urinalysis reveals red blood cell casts and proteinuria. Serum measures of renal function are most commonly normal (112). Antistreptolysin-O and anti-DNAase B titers may be elevated, confirming the diagnosis. Treatment is supportive, however, microscopic hematuria can persist for up to 2 yr. Other glomerular causes of hematuria include Schönlein-Henoch purpura, chronic glomerulonephritis, systemic lupus, Alport's syndrome, and benign familial hematuria. Benign familial hematuria is a very common cause of asymptomatic microscopic hematuria. Family history is helpful, and the physical examination and laboratory investigations are usually normal. Benign familial hematuria is passed by means of an autosomal-dominant route (84,112).

Renal interstitial hematuria may be caused by infection, medications, or toxins, or it may be metabolic, anatomic, or neoplastic. Pyelonephritis is a common cause of interstitial hematuria and resolves as the infection clears. Nephrocalcinosis resulting from idiopathic hypercalciuria is one of the most common metabolic causes of interstitial hematuria. Ultrasound evaluation of these patients demonstrates increased echogenicity, particularly in the medulla. Treatment is based on the underlying cause. The most common medications that cause interstitial hematuria are nonsteroidal anti-inflammatory drugs, and hematuria usually resolves after discontinuing the medication. The most common anatomic abnormality associated with hematuria is renal cyst disease. Treatment for renal cyst disease is, for the most part, supportive. Renal tumors were discussed previously in this section. The two main vascular causes of hematuria are sickle cell trait and disease and trauma. Children

Table 5
Causes of Hematuria

Glomerular
Interstitial
Vascular
Genitourinary
Acute GN
Pyelonephritis
Trauma
UTI
Schönlein-Henoch purpura
Nephrocalcinosis
Renal vessel thrombosis
Urethrorrhagia
Systemic lupus
Nephrotoxins
Sickle cell trait/disease
Nephrolithiasis
Amyloidosis
Acute tubular necrosis
Nutcracker syndrome
Tumors

GN, glomerulonephritis;
UTI, urinary tract infection.

with sickle cell trait or disease have a 1% incidence of gross hematuria and approximately a 15% incidence of microscopic hematuria. Of note, the hematuria associated with sickle cell disease is usually painless and episodic. Sickle cell disease can lead to glomerular scarring and interstitial fibrosis, otherwise known as sickle cell nephropathy. Idiopathic urethrorrhagia, manifested by postvoid dripping of blood from the urethral meatus, blood spots in the underwear, and occasionally dysuria, are a particular concern to peripubertal males. Although the cause is unclear, the condition resolves spontaneously. Hematuria is generally a symptom that needs to be investigated but is generally self-limiting with no long-term sequelae (112).

Urinary Tract Infection

Children commonly are seen by pediatricians or in the emergency department with signs or symptoms of urinary tract infection. These include failure to thrive, fever, irritability, dysuria, enuresis, foul-smelling urine, and hematuria. It is estimated that up to 60% of neonates and

up to 30% of older children who have a febrile urinary tract infection have some underlying genitourinary abnormality (113,114).

Therefore, development of a urinary tract infection requires treatment and follow-up in all children. Initial treatment will depend up the results of the urine culture. The child should continue antibiotic prophylaxis pending radiologic evaluation. This evaluation should include a renal/bladder ultrasound, VCUG, and renal scan (114). These radiographic studies should be deferred until the child is afebrile and has a normal urine culture. In the sick child, collection of urine via midstream or bag specimen should be avoided because it is unreliable. In these children, catheterization with a small-caliber catheter is the preferred manner of urine collection (115). Treatment of any genitourinary abnormality is based on the specific anomaly. The child should remain on antibiotic prophylaxis throughout the evaluation. Prophylaxis should be amoxicillin for the neonate less than 3 mo of age and preferably trimethoprim-sulfamethoxazole or nitrofurantoin for those children older than 3 mo.

Bladder Exstrophy and Cloacal Exstrophy

Bladder exstrophy (Fig. 9) occurs in approx 1 in every 10,000 to 50,000 live births (116). Most children with bladder exstrophy are diagnosed at birth, despite knowledge of antenatal sonographic findings (117). Associated findings include a wide pubic diastasis, a high incidence of inguinal hernia, and an approx 90% incidence of VUR after bladder closure (Fig. 10). With the exception of the exstrophied bladder, these children are healthy. Before the 1970s, treatment was usually urinary diversion. However, beginning in the 1970s, Jeffs and others began to perform staged reconstruction for these children (118). Today, the bladder can remain intact in most of these children. These patients should be cared for in a center of excellence, where exstrophy reconstruction is common. Bladder reconstruction is highly successful, as measured by continence interval and the ability of these children to later have satisfactory sexual relations. The most popular method is a staged reconstructive strategy (119). This involves bladder and abdominal wall closure, with osteotomy in children over 72 hr old (Fig. 11). In males, the epispadias is usually repaired at about 1 yr of age. When the child is ready to achieve continence, bladder neck reconstruction with ureteral reimplantation is performed. An alternative method of reconstruction combines the first two stages into one operation, as described by Grady and Mitchell (120). If adequate bladder capacity fails to develop either after primary or secondary reconstruction, bladder augmentation



Fig. 9. Classic bladder exstrophy in newborn male.

with or without bladder closure and a catheterizable abdominal stoma is the best alternative (121).

Cloacal exstrophy (Fig. 12) occurs in approx 1 in every 250,000 to 400,000 live births (77,122). In addition to the abdominal wall and bladder defects seen in classic bladder exstrophy, omphalocele (95%) and exstrophy of the large bowel, which is sandwiched between two hemibladders, are also present. In addition, there is usually prolapse of the ileum. Up to 75% of these children can also have associated neural tube defects (Fig. 13) (122). Reconstruction is extremely difficult and requires a multidisciplinary plan; however, many children can achieve continence with this approach (123). An attempt should be made to save as much bowel as possible at the time of bladder and omphalocele closure. Males may also need to undergo gender reassignment as a result of the markedly shortened and separated erectile bodies (122).

Myelodysplasia

One of the most fascinating groups of children to follow is that group born with myelodysplasia (Fig. 13). These children can demonstrate a full spectrum of neurogenic bladder dysfunction (124). With the advent of routine prenatal ultrasound and maternal folic acid supplementation, the incidence of children born with myelodysplasia has decreased. Myelodysplasia was once one of the more common causes of neuro-



Fig. 10. Sleep cystogram in child who underwent prior bladder closure. There is high-grade reflux bilaterally.

genic bladder. Once the spinal cord defect has been closed, the genitourinary tract should be evaluated. This includes the use of renal/ bladder ultrasound, VCUG, and urodynamics testing. Up to 5% of children with myelomeningocele have VUR. Urodynamics testing is important to rule out sphincter dyssynergia and uninhibited bladder contractions. This may allow the urologist to predict which patients may have upper tract deterioration in the future (124). In addition, postvoid urine should be measured; the results may prompt voiding by Crede's method or by clean intermittent catheterization.



Fig. 11. Child after bladder exstrophy repair and bilateral osteotomies. Use of a fixation device has replaced the use of modified Buck's traction for these children.



Fig. 12. Newborn female with cloacal exstrophy. Note the omphalocele and disproportionately sized hemi-bladders situated on either side of a portion of bowel.



Fig. 13. KUB of child with cloacal exstrophy. There is a wide pubic diastasis. In addition, the child has spinal dysraphism.

This population of patients is interesting because of the changes that occur in bladder dynamics as the child grows. Spinal cord growth and possible tethering can determine changes in bladder function. Normal reflex voiding, dyssynergic voiding, flaccid bladder, and a spastic bladder may occur in the same child over time (125). It is crucial to follow these patients throughout their childhood. Management of these patients can include observation, clean intermittent catheterization, and the use of anticholinergic medications. Patients with lipomeningocele or sacral agenesis should undergo similar evaluation and follow-up.

Imperforate Anus

This group of children has a form of a cloacal lesion that can be as mild as anal stenosis, requiring only dilation, or as serious as supralevator lesions with rectovaginal or rectocloacal fistulae in females and rectourethral or rectovesical fistulae in males (122).

In 1987, McLorie et al. presented their experience with 484 patients with imperforate anus. They found that the incidence of genitourinary abnormalities was 60% in high lesions and 20% in low lesions (126). The most common genitourinary abnormalities were VUR, renal agenesis, renal dysplasia, neurogenic bladder (as a result of either a concomitant vertebral anomaly or bladder denervation that occurred during rectal pull-through), and cryptorchidism (127,128). The evaluation of these children should always include a renal and bladder ultrasound to evalu-

ate the upper and lower tracts, VCUG looking for the location of the fistula and for the presence of VUR, and urodynamic testing for any patient with a supralelevator lesion or evidence of vertebral anomalies. Many of these children are treated emergently with fecal diversion, with reconstruction occurring later. DeVries and Pena originally described the treatment of the imperforate anus in 1982 (129). These authors pioneered a posterior sagittal approach that is still the preferred method of rectal pull-through. In addition, patients undergo fistulectomy at the time of the pull-through procedure.

Prune-Belly Syndrome

Prune-belly syndrome, also known as Eagle-Barrett syndrome and triad syndrome, is manifested by deficient or absent abdominal wall musculature, urinary tract dilation, and cryptorchidism (Fig. 14) (130). This syndrome occurs almost exclusively in males, with a female variety being described by Hirose in 1995 (131).

There is a wide spectrum of this syndrome, ranging from normal renal function to *in utero* death. This syndrome has three broad categories. Children with urethral obstruction, oligohydramnios, and Potter's syndrome-type facies comprise the first group. Death in this group is usually the result of pulmonary hypoplasia. The second group is characterized by mild renal impairment, although renal failure may develop in the future. The last group has normal renal function (132). Urologic evaluation of children with prune-belly syndrome should include renal and bladder ultrasound, VCUG, and furosemide renal scan to assess differential function and adequacy of upper tract drainage. About 50% of patients have a patent urachus. These children should be started on antibiotic prophylaxis at birth. Treatment is individualized; however, there is little debate regarding the need for bilateral orchiopexy. This can be accomplished either laparoscopically or by an open procedure (133). Despite early orchiopexy, these children are unable to father children. However, there is evidence to suggest that there are spermatogonia in the testes of these children, opening the possibility of assisted reproductive techniques for this population (134). Other surgical treatments described include abdominoplasty, reduction cystoplasty, and bilateral ureteral reimplantation.

Urethral Prolapse

Urethral prolapse is found predominantly in young African-American females. Often treatment is sought because of vaginal bleeding or pain. Occasionally these children will be referred to the gynecologist. On examination, these girls have protrusion of the urethral mucosa, and



Fig. 14. VCUG of a child with prune-belly syndrome. Note the diffuse dilation of the lower genitourinary tract, which is part of the classic triad.

the mucosa will most often be hyperemic and friable. Conservative treatment with local estrogen cream and sitz baths usually allows complete resolution. However, for those girls who do not respond to conservative therapy, surgical excision of the prolapsed mucosa is curative. The differential diagnosis of an introital mass includes ureterocele prolapse and sarcoma botryoides; therefore, careful inspection is warranted to confirm the diagnosis of urethral prolapse (35,101).

SUMMARY

This section has been devoted to an overview of conditions that require emergent or urgent evaluation and treatment. Often pediatric urologists are called on to evaluate these children because emergency medicine physicians, pediatricians, or parents perceive an emergency. It behooves us to see these children, begin the appropriate evaluation, reassure the consulting physicians, and allay the fears of the parents and children. The majority of the conditions discussed will be found in greater detail in other sections.

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3

Vesicoureteral Reflux

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INTRODUCTION

Vesicoureteral reflux (VUR) continues to define the practice of pediatric urology. VUR, or retrograde flow of urine from the bladder to the kidney, was identified in humans more than 100 years ago by Pozzi (1).

Technical advancements and critical assessment have improved our understanding of the pathologic process of VUR, allowing us to refine management and diminish morbidity. However, the decision to use medical vs operative management and the appropriateness of a particu-

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lar technique remain variable and controversial. This chapter will highlight the epidemiology, cause, evaluation, and management of VUR.

EPIDEMIOLOGY

Although VUR is considered normal in some animals, it is not normal in humans (2,3). The prevalence of VUR is unknown but it likely occurs in 0.4–1.8% of asymptomatic children (4). The incidence of VUR is significantly increased in children who have symptomatic urinary infections and is reported to be 30–50% (5–13). VUR has been reported in 0.6% of asymptomatic neonates, one-third of whom will have the antenatal diagnosis of hydronephrosis (9,14). Hereditary factors play a role, with 30–45% of asymptomatic siblings having VUR, and 60% of children having one parent with VUR (15,16). Because of the natural history of resolution, the incidence of VUR in siblings is directly related to their age at the time of evaluation, especially when the sibling in question is older than the index case (15,17). The severity of the index patient does not correlate with the degree of disease noted in the sibling (15). The exact mechanism of inheritance is unknown, but it is presumed to be polygenic and multifactorial (18). The incidence of VUR in twins and offspring supports an autosomal-dominant mode of inheritance (15,17). Investigation of the PAX gene may shed light on the influence of genetics in VUR, with mutations in PAX-2 genes associated with VUR (19,20).

The prevalence of VUR appears to cross racial lines, as pointed out in the early 1970s by Kunin (21). VUR occurs in African Americans at a rate one-tenth the rate in asymptomatic whites and one-third the rate in symptomatic whites (22,23). In a recent review of neonates with antenatal hydronephrosis, there were no African-American children with VUR (24). Although there is a difference in overall incidence between races, there was no significant difference in the mode, age when treatment was sought, or subsequent outcome, as reported by Skoog and Bellman (25).

It is well understood that the frequency of VUR is inversely proportional to age in both symptomatic and asymptomatic children. VUR has been identified in 70% of symptomatic children under the age of 1 yr, compared with only 25% of symptomatic children between the age of 1 and 4 yr (26).

Gender analysis shows that VUR occurs in girls older than the age of 1 yr four to five times more often than in boys of the same age (27–31). However, hydronephrosis is diagnosed in males three to six times more often than in females (32–38). In addition, high-grade neonatal VUR is

strongly associated with male gender, possibly because of increased outlet resistance (32,39).

PATHOPHYSIOLOGY

A framework of normal anatomy is helpful to understand the pathophysiology of VUR. The distal portion of the ureter is divided into the juxtavesical ureter and the terminal ureter. The terminal ureter subsequently separates into the intramural and submucosal components (40). The ureter is enclosed in a poorly defined, loose sheath beneath the peritoneum, which protects the adventitia from neoplastic and inflammatory processes. Proximally, the ureteral sheath and adventitia become continuous with the renal pelvis. Distally, the sheath and ureteral adventitia join to form Waldeyer's sheath, which extends into the bladder wall as a portion of the deep trigone (40).

The ureter is made up of three layers: adventitia, muscular coat, and mucosa. The adventitia consists of longitudinally running collagen fibers (41). The adventitia, along with the outer sheath, is loosely attached to the muscularis, allowing for peristaltic activity. The muscularis is made up of smooth muscle cell bundles interspersed with collagen. These bundles are arranged in three distinct layers: interlongitudinal, middle circular, and outer longitudinal (42). As the ureter begins to enter the bladder, the muscular configuration changes into longitudinally oriented fibers. Ureteral mucosa consists of multiple layers of transitional epithelium directly overlying the lamina propria. The ureters are supplied by a vast anastomotic arterial network. The proximal blood supply originates from the renal artery, and the middle spindle is supported by branches from the gonadal artery. The distal ureter receives blood from the internal iliac and the superior and inferior vesical arteries (43).

The ureter passes into the bladder and through the trigone in an oblique fashion, allowing for compression of the intramural ureter and opposition of the epithelial lumen. The normal intravesical tunnel elongates from birth through adulthood and is estimated to be between 0.5 and 1.3 cm. The final intravesical length is achieved in early puberty (44). Normally, the tunnel prevents the retrograde transport of urine (i.e., reflux) but not the antegrade propulsion of urine from a peristaltic wave. The location of the ureteral orifice relative to the trigone and lateral wall is directly associated with the presence of VUR. If the ureter inserts on the lateral wall, the orifice will have the configuration of a golf hole. The lack of tunneling results in no opposition of the epithelial lumen and therefore free reflux of urine, particularly when the bladder begins to fill

and expand. Abnormal trigonal development also leads to lateral displacement and migration of the ureteral orifice (45).

Mackie and Stephens (45a) have suggested that not all renal dysplasia is caused by inflammatory change. They theorized that the abnormal insertion of the ureter is caused by a misplaced ureteral bud, resulting in lateralization of the ureteral orifice and simultaneous proximal ureteral induction of polar metanephric blastema, causing segmental renal dysplasia (46,47). The finding of completely duplicated systems with an ectopic upper pole ureter associated with a dysplastic upper segment provides support for this theory. This theory is also supported by the finding of a single system with high-grade VUR and renal dysplasia in an asymptomatic neonate undergoing evaluation of antenatal hydronephrosis.

VUR may be primary or secondary. Primary reflux is caused by factors described above. Secondary reflux is related to prolonged increased intravesical pressure caused by an obstructive process such as posterior urethral valves, ureteroceles, neurogenic bladder dysfunction, or dysfunctional voiding. Inflammation and edema can lead to changes of the trigone and bladder wall, allowing VUR to occur during an inflammatory process.

REFLUX NEPHROPATHY

In the early 1970s, Bailey (48) described the association of chronic atrophic pyelonephritis and VUR, which subsequently became known as reflux nephropathy (Fig. 1).

Reflux nephropathy has been reported to occur in approx 0.3% of the white population, and in 30–60% of all children with VUR (49). Until recently, reflux nephropathy and chronic renal scarring were presumed to be caused by the co-existing factors of VUR, intrarenal reflux, and urinary infection. Ransley and Risdon reported the “big bang theory,” which suggested that renal parenchymal changes could be caused by a single urinary infection (50).

Renal scarring was theorized to be the result of the host inflammatory response caused by the infecting pathogens and that it occurred most often in polar regions because of complex renal papillae that facilitate intrarenal reflux (Fig. 2).

Pyelonephritis is now recognized in nonrefluxing systems. This may be the result of hematogenous infections, which are seen more often in infants; bacterial adherence associated with p-fimbria; or inflammatory trigonal changes (1). Segmental renal scarring can occur with sterile



Fig. 1. Chronic atrophic pyelonephritis resulting in a small, contracted, scarred kidney. This is now known as reflux nephropathy.

urine in extreme conditions of elevated bladder pressure. As indicated above, infection is not the sole cause of parenchymal changes consistent with reflux nephropathy. Asymptomatic neonates undergoing screening for antenatal hydronephrosis are often noted to have high-grade VUR and upper tract changes (51–55).

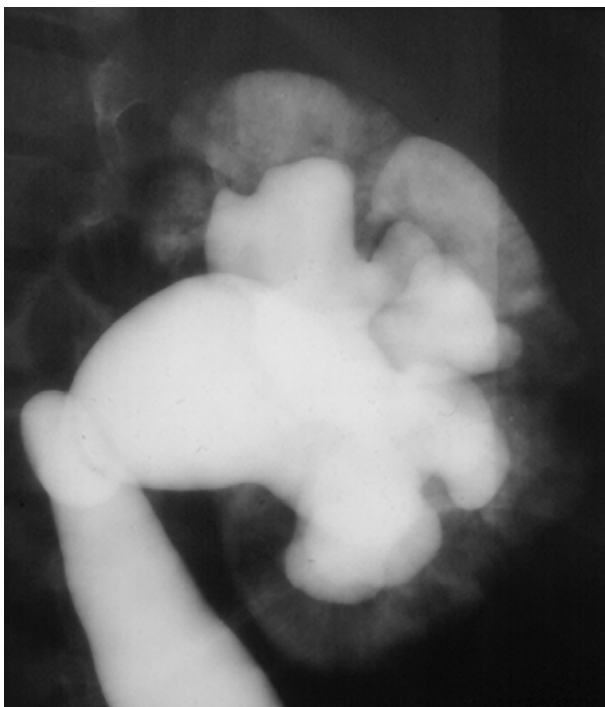


Fig. 2. Grade V/V VUR with intrarenal reflux.

EVALUATION

Urinary Tract Infection (UTI)

Prior to an invasive evaluation, children must be confirmed to have clinically significant bacteriuria. Positive urine culture is defined by more than 100,000 colonies of a single organism found in two successive bag specimens that have been placed for less than 20 min; or in two successive clean voided specimens.

A catheterized specimen or suprapubic aspirate showing more than 5000 colonies of bacteriuria is significant. Once UTI is confirmed, symptoms, gender, and age of the child are factors that determine the treatment. UTIs in boys occur most often within the first year of life and are strongly associated with the presence of the foreskin. Whether circumcised or not, however, boys who experience a single, symptomatic UTI should be evaluated with diagnostic imaging. In girls, imaging is often

deferred after their first UTI (56–58). However, from a practical point of view, imaging in a young girl is appropriate after a first UTI. This is based on the recurrence rate of UTIs in girls, which is estimated to be approx 30% within the first year and 50% within 5 yr. The importance of early imaging is supported by data showing renal scarring in 5–17% of children after their initial infection (59–62).

African-American children have a lower incidence of reflux (10%) and renal scarring (23%) than white children (21,23,63,64). However, recurrence of UTIs continues to be a problem for all children regardless of ethnicity, and therefore, it is important to perform diagnostic imaging on all children after their first infection to identify those at risk for recurrence.

Antenatal Hydronephrosis

There is a consensus that neonates with persisting hydronephrosis benefit from undergoing a voiding cystourethrogram (VCUG). It has been questioned whether neonates with a normal upper urinary tract on sonography benefit from lower urinary tract evaluation. Support for lower urinary tract imaging comes from reports of reflux occurring in 10–25% of neonates with a normal upper tract whose antenatal sonogram showed a dilated renal pelvis larger than 5 mm (65–69). However, when the upper urinary tract is normal, low grades of VUR are identified and resolution is very likely. Therefore, some physicians have recommended against lower urinary tract imaging unless the infant becomes symptomatic (70,71).

Familial Reflux

VUR occurs in 30–50% of siblings, with boys having a slightly decreased incidence (72–78). VUR has been reported in 66% of both twins and offspring of a parent with reflux (15,17,79). The age of the sibling and that sibling reflux appears to follow a more benign course should be factors in the choice of diagnostic study (80). Based on Smellie's (80a) work, it has been found that new renal scarring can develop through the age of 10 yr, but children younger than 5 yr are at the greatest risk.

Therefore, asymptomatic siblings under the age of 5 yr should be screened with a VCUG. Siblings older than 5 yr could be initially screened with sonography, with the knowledge that low grades of reflux would be missed. In an older sibling with no prior urinary infections, the presence of reflux would not lead to operative or medical therapy. Therefore, definite knowledge of reflux is not clinically significant.

ASSOCIATED CONDITIONS

VUR is associated with other urinary problems such as renal agenesis, horseshoe kidney, renal ectopia, multicystic dysplastic kidney (MCDK), renal duplication, ureteropelvic junction (UPJ) obstruction, and ureteroceles. Renal agenesis and MCDK, in particular, have high rates of contralateral VUR (81–84).

DIAGNOSTIC EVALUATION

Voiding Cystourethrogram

The diagnosis of VUR is classically made based on results of the VCUG (Fig. 3). VCUG is important because 23% of children with VUR have normal upper urinary tract imaging on sonography or on a dimercaptosuccinic acid (DMSA) scan (85). The voiding component of the cystogram is essential, with data showing that 25% of children reflux only during voiding. Therefore, an anesthetic cystogram with or without suprapubic compression is not adequate to diagnose VUR. When there is a high suspicion of VUR, especially in patients with renal duplication or an ectopic ureter, a cyclic VCUG can have a higher yield for identifying reflux, particularly when the ureteral orifice is located within the bladder neck (86–88).

The two common techniques for VCUG are conventional fluoroscopic imaging and radionuclide cystography (Fig. 4). Conventional fluoroscopy is advantageous because it can be used to quantify the degree of reflux based on anatomic upper tract changes, to identify low-grade VUR, to evaluate ureteral insertion, and to assess the anatomy of the bladder, bladder neck, and urethra. Anatomic evaluation is particularly important when imaging boys for the first time to rule out urethral obstruction. Conventional cystography, however, does expose the gonads to radiation, especially the ovaries. Gonadal exposure from typical cystography has been reported to be 0.21 rads but is dependent on the overall fluoroscopic time and number of films taken (89). The radionuclide cystogram is a more sensitive and accurate method for diagnosing VUR because it allows for continuous monitoring of the bladder during all phases of filling and voiding (90). In addition, this method significantly decreases the amount of radiation exposure, particularly to the ovaries. The reduction has been reported to be 200-fold compared to conventional cystography (88,91,92). Newer technology allows for tailored conventional cystography using digital fluoroscopy. This combines the advantages of documenting anatomy and limiting gonadal

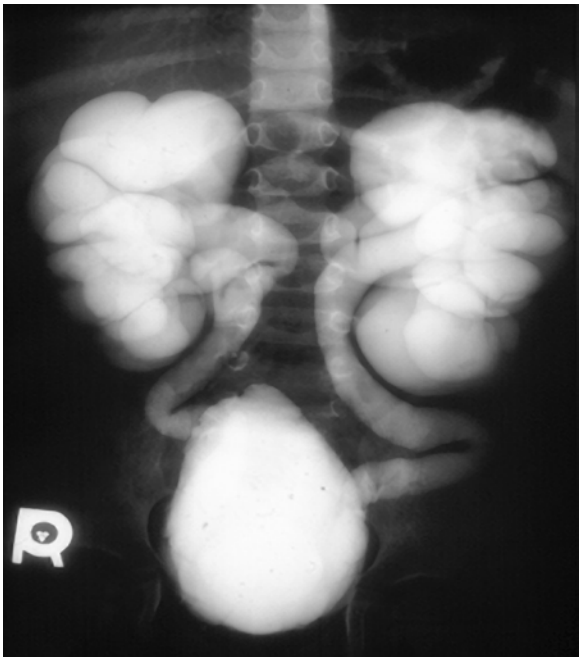


Fig. 3. Conventional VCUG showing bilateral grade V/V vesicoureteral reflux.

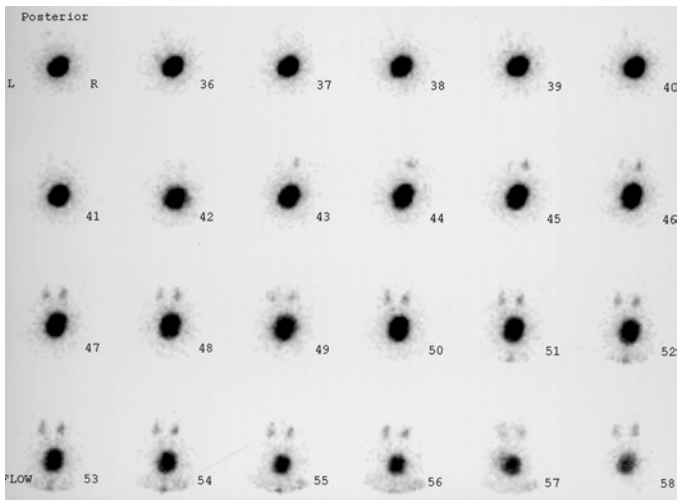


Fig. 4. Radionuclide cystography with Tc 99m pertechnetate. Note the presence of vesicoureteral reflux that could not be graded by IRS classification.

radiation exposure (91). Indirect cystography has been reported using other radionuclide agents. It is advantageous because it is less invasive, but it has not gained wide acceptance. Investigative techniques using sonicated beads and sonography eliminates the risk of radiation and may hold promise in the future (93–97).

Timing of the VCUG relative to the onset of a UTI remains controversial. Performing the study during an active UTI can result in increased morbidity. Edema from inflammation can prevent the identification of VUR when the study is obtained at the onset of symptoms. On the other hand, a small group of children only reflux when infected. Weighing all the factors, it appears that lower tract imaging can be obtained when most practical and convenient for the family, provided symptoms have abated and appropriate antibiotics are given (98).

Upper Tract Assessment

In the past, intravenous urography was the standard for assessment of the upper urinary tract. In children, however, it has been replaced by renal sonography. Sonography provides assessment of renal size, cortical medullary differentiation, echogenicity, and hydronephrosis and affords evidence of significant scarring. The lack of radiation exposure and noninvasive characteristics make this study particularly appealing for the pediatric population. Color Doppler imaging has been reported to improve the accuracy of the VCUG in detection and grading of VUR (99).

When assessing the upper tract for renal scarring, the DMSA renal scan has proven to be the most accurate modality. Standard DMSA imaging can be enhanced using single photon emission computed tomography assessment, which increases the sensitivity of identification of scarring but may not be of practical significance (30,100). Parenchymal defects noted immediately after an episode of pyelonephritis may be the result of acute inflammation and may not represent a renal scar. A true scar should be confirmed approx 6 mo after the inflammatory event (101).

CLASSIFICATION

Multiple classification systems are used to describe VUR, and each has its own idiosyncrasies. As a result, most pediatric urologists and radiologists have adopted the classification system used by the Inter-national Reflux Study (IRS) (Fig. 5) (102). This system is based on the work of Heikel and Parkkulainen and Dwoskin and Perlmutter (103,104). The greatest use for a standardized classification system is to allow consistent transfer of information regarding a patient's problem.

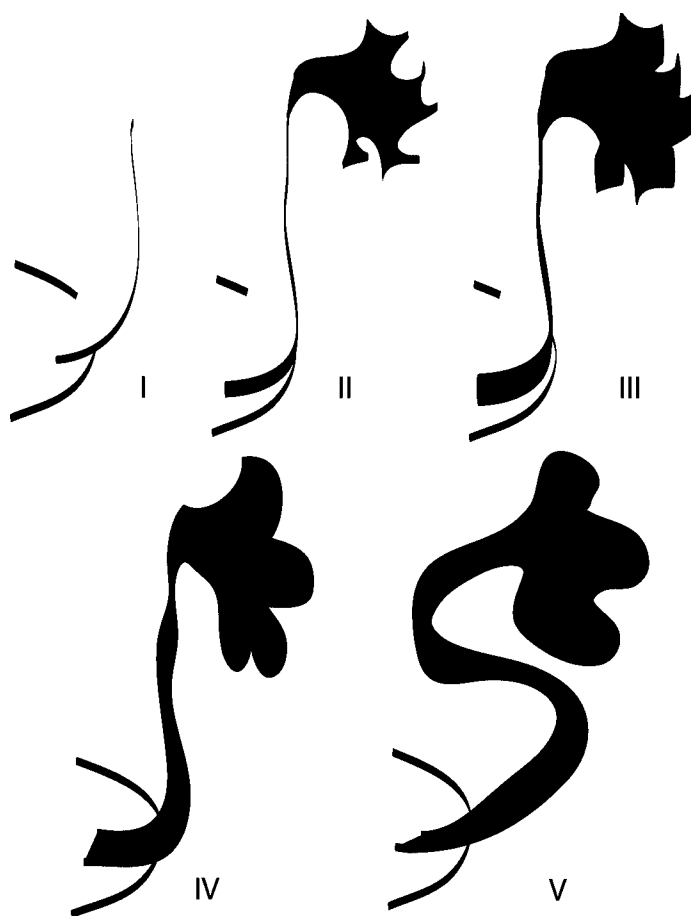


Fig. 5. International Reflux Study classification: grade I, contrast present in the ureter; grade II, contrast ascending to the renal pelvis without distortion; grade III, mild ureteral dilation with a full renal pelvis and flattening of the renal pyramids; grade IV, bulging of the ureter with mild tortuosity, enlargement of the renal pelvis with widening of the infundibulum, and effacement of the renal pyramids; grade V, significant tortuosity and dilation of the ureter with significant renal pelvic enlargement, distention of the infundibulum, and loss of caliceal impression.

The IRS classification has been extrapolated to describe results from the radionuclide cystogram. However, it is very difficult to discern the different grades because of the diminished anatomic detail noted on nuclear imaging and because of the potential for “bloom” effect, which may cause overestimation of the grade of reflux. When reporting results of

the radionuclide cystogram, it is most appropriate to use the simplified classification presented by Willi and Treves (105). This is a three-component scale, with grade I corresponding to IRS grade I, grade II corresponding to IRS grade II and III, and grade III corresponding to IRS grade IV and V.

The degree of VUR can vary among studies and may be subject to the study technique. Variation can occur as the result of the volume of contrast or radiopharmaceutical media placed in the bladder relative to the child's estimated bladder capacity, the cooperative nature of the child, the ability of the child to void, and cyclic assessment.

COOPERATIVE STUDIES

Multi-institutional studies have been undertaken to determine the outcome of medical vs operative intervention. The most quoted studies are the Birmingham (UK) Cooperative Study and the IRS in Children (106–108). Concerns with both studies are related to patient enrollment, comparison of the grade of reflux, and differences in operative technique. However, given those limitations, both studies have provided beneficial information. The Birmingham Cooperative Study followed children for 5 yr who had higher grades of reflux or previous renal scarring. Comparisons were made between children who received prophylactic antibiotics or underwent operative intervention. There was no significant difference between medical and operative management when assessing breakthrough urinary infections, renal function, renal growth, progression of renal scarring, or the onset of new scarring. Breakthrough infections occurred in approx 25% of children in both groups, but the clinical significance of the infection was not clear and it was not known whether the infections were caused by cystitis or pyelonephritis.

The general conclusion from this study was that medical and operative management offer the same degree of protection when looking at renal function and scarring.

The IRS included centers throughout Europe and the United States. Children under the age of 10 yr who had IRS grades III/V and IV/V VUR were evaluated. The resolution of VUR in children treated medically was 80% for grade III/V and 25% for grade IV/V. Unilateral reflux resolved more often than bilateral reflux. There did not appear to be a gender bias (109). New onset of renal scarring occurred in 16% of children, most of whom were under age 5 yr and all of whom had breakthrough urinary infections (110–116). The operative outcome for correction of VUR was very successful, with limited complications.

Overall, pyelonephritis occurred less often in the medically treated group than in the operative group, but the incidence of renal scarring (17%) was the same in both groups. Contemporary results regarding renal function and urinary infection are similar to those of cooperative studies showing no difference between medical and operative management in children with bilateral VUR (117–120). However, renal scarring may be decreased with operative intervention (121,122).

The cooperative studies found that reflux resolved in 20–30% of children over a 1- to 2-yr period. This has been substantiated by other retrospective data (109,123–126) and provides support for limiting the frequency of VCUG to every 1 to 2 years. Imaging performed more frequently is not justified based on morbidity, cost effectiveness, and radiation exposure. It has been recommended that two successive normal imaging studies be performed to ensure resolution of reflux. This recommendation is based on data showing that 30% of children have persisting reflux even though a prior imaging study was reported to be normal (122,127,128). From a practical point, obtaining a second VCUG only in children with persisting symptoms seems appropriate.

PREGNANCY

Reflux during pregnancy has long been thought to carry significant morbidity, resulting in increased rates of pyelonephritis, toxemia, preterm delivery, fetal growth retardation, and decreased maternal renal function (129–135). Asymptomatic bacteriuria occurs in approx 4 to 7% of pregnant women (136). Of those untreated, approx 30 to 40% have progression to pyelonephritis (135,137). The risk of pyelonephritis is approx 50 to 60% when there is previous renal scarring (138,139). It appears that women with a history of childhood UTIs are at the greatest risk.

Whether pyelonephritis occurs more often in women with persisting or corrected reflux remains controversial (140). There is little outcome data related to pregnancy and the beneficial effects of diminished morbidity when correcting VUR (141,142). Urinary infections have been reported to occur in 40–60% of pregnant women who have had reflux corrected, with approx 20% having pyelonephritis. This result is similar to results in pregnant women with persisting VUR.

Current therapeutic agents such as the penicillin and cephalosporin have been used prophylactically in pregnancy without undue morbidity to the woman or the fetus (125). When considering the future issue of pregnancy, the benefits of correcting VUR are likely limited to the child with a higher grade of VUR who has persisting symptomatic UTIs (143).

TREATMENT

The goals of VUR treatment include minimizing short- and long-term morbidity. Short-term problems caused by symptomatic pyelonephritis can be prevented by medical therapy. Long-term preventive measures include medical therapy and operative intervention. The American Urological Association-sponsored clinical practice guidelines on management of VUR should be the working template for conventional therapy of primary problems. Children with grades III/V VUR are generally treated with prophylactic antibiotics after resolution of the initial infection. If the child remains asymptomatic and VUR persists, it is reasonable to continue prophylactic antibiotics through the age of 6 yr. After the age of 6, the risk of renal scarring is diminished, and it is practical to stop prophylactic antibiotics and follow the child's course. Children with persistent episodes of cystitis or a significant episode of pyelonephritis would then be considered for operative repair of reflux. Girls with persisting reflux have more infections than boys when coming off prophylactic antibiotics. However, there does not appear to be any difference in the development of new renal scars between boys and girls, with rates of approx 2% and 4%, respectively (144). When grade IV–V/V VUR is identified, the likelihood of resolution is diminished and operative intervention is practical when compared to continuing long-term prophylactic antibiotics. The exception to this would be identification of high-grade VUR in an infant with the antenatal diagnosis of hydronephrosis. There does not appear to be any advantage to early operative repair of high-grade VUR in infants. Placing infants on prophylactic antibiotics and following them for 1 to 2 yr is appropriate. There is often substantial downgrading of the VUR with time, particularly in boys. No child should be managed purely by a protocol. Individual characteristics of the child's problem and his or her social situation must be considered when developing a treatment plan.

MEDICAL THERAPY

Medical therapy for VUR is based on the premises that VUR resolves or improves with time and that children under the age of 5 yr are at the greatest risk of sustaining upper urinary tract damage as a result of a single or repetitive episode(s) of pyelonephritis. Medical therapy includes administering prophylactic antibiotics and educating the patient and parents about the importance of a healthy diet and perineal hygiene, and about problems associated with the dysfunctional elimination syndrome. Recurrent urinary infections are more problematic in children

who have poor perineal hygiene and fecal problems related to constipation or encopresis. Toddlers progressing through the milestone of toilet training are at the greatest risk (145).

The effectiveness of managing VUR with prophylactic antibiotics was supported by multi-institutional studies in the mid-1970s (146). The use of prophylactic antibiotics appeared to help control short episodes of recurrent UTIs and prevent the long-term sequelae of progressive renal scarring. It is widely accepted that the use of prophylactic antibiotics can prevent the new onset of pyelonephritic scarring. However, antibiotic prophylaxis will not eliminate all renal scarring, including that seen in asymptomatic newborns evaluated for antenatal hydronephrosis and found to have VUR with renal parenchymal defects. Successful continuous prophylactic medication should maintain a low pharmacologic level, minimize disruption in the bacterial flora of the bowel, minimize drug-related adverse effects, and maintain compliance. Effective medications must meet the above goals, cover a broad spectrum of urinary tract pathogens, and remain cost effective. Most pediatric urologists prefer using nitrofurantoin macrocrystals, trimethoprim-sulfamethoxazole (TMP-SMZ), trimethoprim, and occasionally, nalidixic acid. The prophylactic dose is typically one-third to one-fourth the therapeutic dose used to treat conventional cystitis.

Nitrofurantoin macrocrystals have the benefit of rapid absorption from the gastrointestinal tract, with minimal medication entering the descending and sigmoid colon. This decreases the common problem of developing recurrent urinary infections because of resistant bowel flora and perineal contamination. Although nitrofurantoin is excreted in the urine at high concentration, tissue uptake is poor, and formal treatment of pyelonephritis is less efficacious and not recommended. Because tissue uptake is limited, there is limited secretion in vaginal and perineal tissue, minimizing bacterial overgrowth and resistance. The nitrofurantoin suspension commonly prescribed for infants and toddlers is often poorly tolerated because of its bad taste and common side effects of nausea, vomiting, gastrointestinal irritability, headache, and dizziness (147). The macrocrystals reduce those side effects and are well tolerated even in small children. The accepted dosage of nitrofurantoin macrocrystals is 1–2 mg/kg given once a day. Nitrofurantoin should not be given to neonates less than 2 mo of age because of the potential for hemolytic anemia. Its use should also be avoided in children with G6PD deficiency.

TMP-SMZ is an appropriate alternative to nitrofurantoin. Problems related to the long-term use of TMP-SMZ are limited. The most com-

mon side effects of urticaria, neutropenia, thrombocytopenia, and eosinophilia have been reported in approx 40% of children treated long-term. An increased risk of dental caries has been reported in 5% of children and was thought to be the result of the sugar preparation of the suspension. This problem can be decreased by advising routine dental brushing, especially after taking the suspension (139). Any child on long-term TMP-SMZ therapy should undergo complete blood count testing every 6 mo. Hematologic problems should normalize quickly after the medication is stopped.

OPERATIVE INTERVENTION

The most difficult aspect of surgical intervention relates not to the technique but to the decision regarding who benefits from operative intervention. Once the decision is made, open techniques, whether intravesical or extravesical, are highly successful and well tested. The use of minimally invasive endoscopic techniques is on the rise, with encouraging results.

Cystoscopy has played an historic role in evaluating VUR and determining the benefits of correction. Cystoscopy can be helpful in identifying unexpected anatomic problems such as an unrecognized duplicated system or locating the orifice of an ectopic ureter. In boys, visualization of the posterior urethra may identify a defect not appreciated on preoperative imaging. In the past, a great deal of emphasis was placed on the location and appearance of the ureteral orifice and its potential to predict the presence of reflux or the possibility of resolution (148). However, no cystoscopic finding, whether normal or abnormal, should dictate whether operative management is undertaken. Cystoscopy may provide useful information immediately before undertaking corrective intervention, but it has limited value as an independent procedure, and the decision to operate should be based on the child's clinical course (149).

Before any procedure is undertaken, urinary infections must be cleared and voiding dysfunction should be treated. Children with a functional elimination syndrome should be placed on an aggressive bowel control regimen (150,151). When necessary, an open repair remains highly successful, even in children with persistent bladder instability (152).

Intravesical Techniques

The bladder can be exposed in a variety of ways. A low transverse incision is cosmetically acceptable, provides an excellent exposure, and results in limited morbidity. Once the bladder is open, there are several

options for correcting reflux. All are based on the principle of mobilizing enough ureteral length without devascularizing the distal segment and creating a tunneled reimplantation of a ratio of 4–5:1, length of the tunnel to diameter of the ureter. The Politano–Leadbetter technique has stood the test of time, with success rates approaching 99% (153,154). The ureteral orifice remains in a location that should permit future endoscopic intubation, if needed. The disadvantage of this technique is limited visualization when creating a new hiatus superior and medial to the original site of entrance. Great care must be used to prevent entering the peritoneum and injuring the bowel. The peritoneal lining should be mobilized from the floor of the bladder, allowing the ureter to enter the bladder with minimal angulation. If the position of the ureter is too lateral, obstruction can occur when the bladder fills (152). Paquin's technique is similar to the Politano–Leadbetter procedure, with the addition of an extravesical approach for creating the new hiatus, minimizing the above risks.

Glenn and Anderson recognized the associated problem of creating a new hiatus and popularized a technique of ureteral advancement. The ureter is mobilized intravesically and advanced to a more medial and caudad location without creating a new hiatus (155). The Glenn–Anderson technique has achieved success in approx 98% of cases (156–158). However, the ability to obtain the desired tunnel to ureteral diameter ratio can be limited and is dependent on the original location of the ureteral orifice. Therefore, this technique is best suited for laterally positioned, nondilated ureters.

Cohen overcame the limitations of the Glenn–Anderson repair by mobilizing the ureter intravesically and creating a tunnel across the trigone. This easily accomplishes the goal of creating a 4–5:1 ratio of tunnel to ureteral diameter with nondilated ureters (159). The success rate for this technique has consistently been reported to be greater than 98% (160–162). Although the cross-trigonal technique is now the most widely accepted intravesical technique, there is concern about the ability to use a rigid endoscope to cannulate the ureter. Newer technology, including the use of flexible endoscopic equipment and percutaneous suprapubic exposure, should minimize this problem.

With any technique, attention to detail and hemostatic control are important, helping to minimize hospitalization without jeopardizing clinical outcome or increasing patient morbidity.

Extravesical Techniques

In an attempt to decrease the morbidity associated with opening the bladder, the use of the extravesical approach, as initially described by

Lich and Gregoir, has been revisited (163–170). The true advantage for the extravesical technique is related to minimal hematuria, decreased morbidity, and enhanced postoperative recovery (171). Interestingly, urinary retention and voiding dysfunction have been noted with this technique, particularly when a bilateral repair is undertaken (169,172,173).

Minimally Invasive Techniques

Subtrigonal injection is recognized as an efficacious minimally invasive technique for the treatment of VUR. Puri and O'Donnell have popularized this technique and report a success rate of 80–90% (174–177). Enthusiasm for subtrigonal injection is only limited by the injectable agent. Puri's and O'Donnell's success is based on the use of polytetrafluorethylene, which has been reported to migrate as a result of lymphocytic phagocytosis (178). Polytetrafluorethylene is not available for use in the United States. Many other agents have been tested, with limited success (175,179,180). The use of autologous cartilage has shown promising initial results (181,182). Dextranomer/hyaluronic acid copolymer recently achieved Food and Drug Administration approval, but long-term studies are limited (183). Laparoscopic techniques have been explored but as yet have not shown a substantial advantage over open procedures (184).

Megaureter

The megaureter (diameter greater than 8 mm) requires tapering to achieve the desired 4–5:1 tunnel to diameter ratio. Hendren's technique of formal excisional tapering has stood the test of time (185). Hendren tapers the ureter loosely over a 10 or 12 Fr catheter. Care is taken to excise an avascular segment of the ureter. The ureter is closed in two layers, using a running, locking 5-0 or 6-0 absorbable suture. The running layer is discontinued a short distance from the distal end of the ureter. The very distal portion of the ureter is closed with uninterrupted sutures. This allows for excision of the distal ureter, if required, without interruption of the running suture line. The ureter is stented for 5–10 d. Only the intravesical and distal portions of the ureter, which extend 1–2 cm beyond the bladder wall, need to be tapered. There should be a gentle transition from the megaureter to the tapered ureter. Proximal ureteral tapering is required in only limited situations (186).

Marginally dilated ureters may be imbricated, which has the advantage of minimizing devascularization of the distal ureter and reducing the risk of urinary leak, obstruction, and the need for ureteral stents. The two most common imbricating techniques are the Starr and Kalicinski

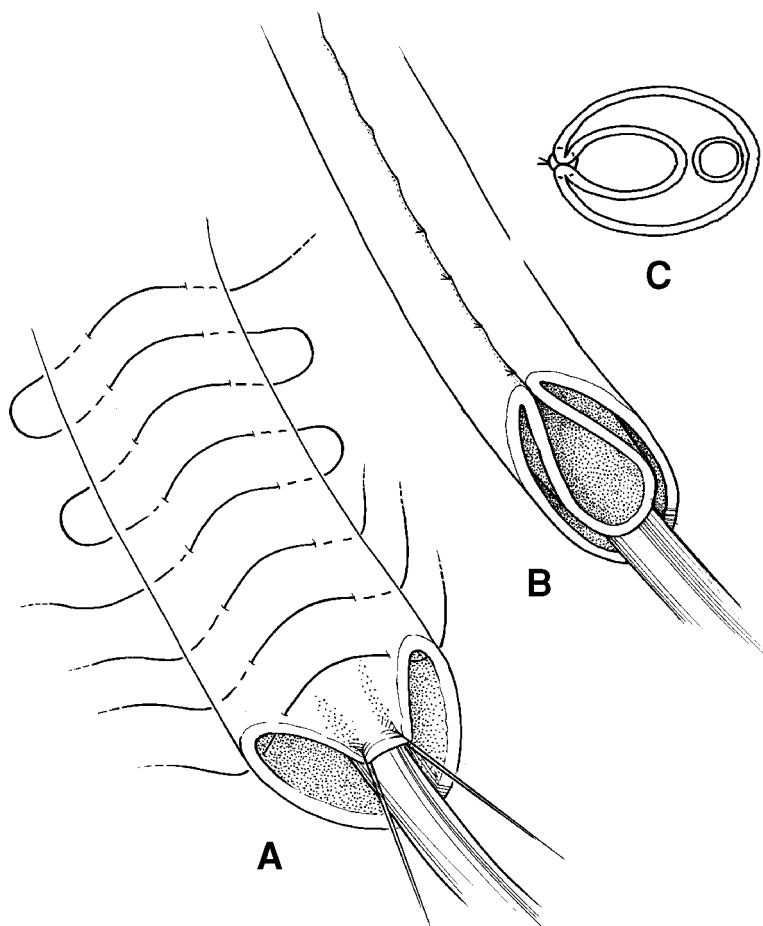


Fig. 6. Starr technique of ureteral imbrication. (A) The ureter is folded using a 10 or 12 Fr catheter as a guide. The distal portion is secured with uninterrupted sutures. (B) Longitudinal view. (C) Cross-section. From ref. 186a.

techniques (187–189). In the Starr technique, Lembert sutures are used to fold in the redundant ureter over a 10 or 12 Fr catheter (Fig. 6) (187). The Kalicinski technique plicates the ureter by excluding the redundant portion from the urinary system (Fig. 7). This is undertaken over a 10 or 12 Fr catheter. The redundant segment is then folded over the outside of the ureter and secured with absorbable sutures (188).

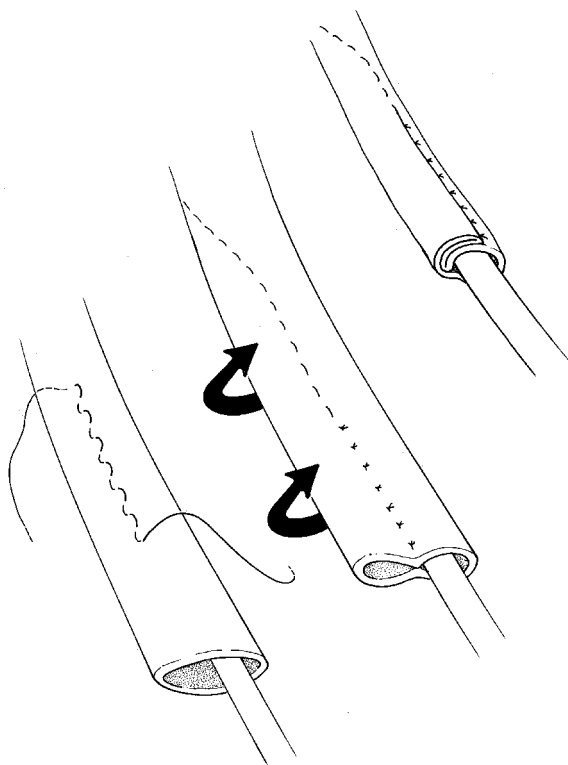


Fig. 7. The Kalicinski technique of ureteral imbrication. The excess segment of ureter is excluded from the flow of urine. It is then folded over the ureter using a 10 or 12 Fr catheter as a guide. From ref. 186a.

POSTOPERATIVE MANAGEMENT

Postoperative morbidity can be limited by adhering to meticulous operative detail; limiting the use of catheter, stents, and drains; and controlling pain. Limiting pain is critical and can be accomplished with the use of caudal anesthesia combined with appropriate analgesic drugs. Ketoralac can decrease postoperative discomfort. Ketoralac is administered in doses of 0.5 mg/kg, with a maximum of 30 mg given every 6 h. Ketoralac use should not exceed a total of eight doses and should be avoided in infants less than 6 mo old. There is some concern about ketoralac because of the potential for increased postoperative bleeding and nephrotoxicity (190). Children must be well hydrated both before and throughout ketoralac therapy. Hydration decreases the risk of neph-

rotoxicity and diminishes problems associated with postoperative bleeding. Ureteral stents and Penrose drains are unnecessary with most procedures. Placement of a urethral catheter is a surgeon's preference. Success has been achieved with overnight placement or with no catheterization. With aggressive intra-operative and postoperative fluid administration, there will be increased urine output. In addition, children who receive caudal anesthesia can be at a greater risk for urinary retention. Therefore, unless a child is to be discharged on the day of the procedure, overnight catheterization is practical (191).

COMPLICATIONS

Obstruction

Ureteral obstruction rarely occurs in nontapered or tapered reimplants. When present, obstruction most often occurs within the first 4 wk following the repair. Because ureteral obstruction can manifest itself silently, imaging the upper urinary tract with renal sonography is appropriate. Obstructive problems are most often caused by kinking of the ureter at the neohiatus or stenosis from distal ureteral devascularization. Endoscopic dilation is possible, but definite treatment with an open repair is best.

Persisting Reflux

Persisting reflux with a nondilated ureter is exceedingly rare after any of the open techniques. Success rates for the dilated ureter have been reported to be approx 95% with imbrication and 54 to 95% with excisional tapering (188,192–201). Reflux noted postoperatively at 6 mo will often resolve with more time, but reflux that persists for longer than 3 yr is unlikely to resolve (191). If significant persisting VUR occurs, corrective intervention is required. A formal reoperative procedure is most appropriate, with attention paid to preserving the ureteral blood supply and maximizing the ratio of ureteral tunnel to ureteral diameter. *In situ* ureteral tailoring is an alternative to formal excisional repair, (199) achieving a gradual decrease in intraluminal diameter without compromising vascularity and avoiding the difficult ureteral dissection. This may be the most beneficial if the ureteral tunnel length was maximized during the first encounter (199).

Contralateral Reflux

Contralateral reflux has been reported in 1.5 to 25% of children undergoing unilateral correction using a variety of techniques (202,203). One factor leading to postoperative contralateral VUR may be a history

of bilateral VUR. When a nontapered ureteroneocystostomy is performed on the contralateral side because of a history of bilateral reflux, postoperative reflux in either ureter is exceedingly rare (1.4%) (161).

FOLLOW-UP

With the success of a standard repair approaching 100%, the recommendation has been made to forgo the postoperative VCUG (204–207). It should be recognized that these outcome data are reported by pediatric specialists who have extensive background and experience treating vesicoureteral reflux. It may be argued that ureteroneocystostomy is not the most challenging endeavor that we perform, but the procedure must be respected. Urologists who perform random and infrequent reimplantation should be assured of their personal outcome before considering the elimination of postoperative VCUG (208).

Long-term follow-up is based on the child's propensity toward further urinary infections and the presence of renal scarring, whether medical or operative intervention was used. Repairing VUR can lessen the occurrence of symptomatic urinary infections, but for some children, particularly those with lower grades of reflux, this may not be the case. Treatment of persisting infection includes long-term multiagent chemotherapy and control of the dysfunctional elimination syndrome. Renal scarring lends itself to a greater risk of hypertension, and therefore, children with renal scarring should have periodic assessment of blood pressure. It is practical to recommend that any child with VUR have his or her blood pressure assessed at least twice a year.

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4

Endoscopic Treatment of Vesicoureteric Reflux

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INTRODUCTION

Endoscopic injection therapy for vesicoureteric reflux (VUR) is now entering its third decade of use. Matouschek originally described the technique using Polytef paste in 1981 (1). O'Donnell published the first large clinical series in which endoscopic injection was used to treat reflux and coined the term STING, an acronym for subtrigonal Teflon injection, to describe the technique (2). Subsequent to this landmark

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publication, other groups accumulated and published their experience with this procedure.

Teflon paste has continued to be used for this indication, but a number of other substances have been applied clinically to achieve the same end. The procedure has an inherent attraction in that it can be performed on an outpatient basis with minimal morbidity and decreased cost when compared with standard ureteroneocystostomy (3,4). Although the surgical concept of the STING is logical and has merit, there are potential drawbacks to the technique, primarily having to do with the materials used to effect it. Currently available materials are suspect because there are no long-term efficacy data and there may be patient safety issues. The ideal injection material should allow for ease of endoscopic delivery and maintenance of its volume with passage of time. Moreover, the material should be biocompatible, nonmigratory, nonimmunogenic, and noncarcinogenic. The quest for the ideal injectable material remains the STING's "Holy Grail." It is the purpose of this chapter to chronicle the evolution of the STING technique and its future challenges.

INDICATIONS

The STING technique evolved as an alternative to ureteroneocystostomy. As a result, the indications for intervention mirror those for the open technique: breakthrough urinary tract infection (UTI) in a patient receiving adequate antibiotic prophylaxis, progression of renal scarring in a patient receiving medical therapy, nonresolution of reflux despite an adequate trial of medical management (> 48 mo), high-grade VUR in a child more than 2 yr of age, and noncompliance with medical management. We believe that the indications for intervention should not conceptually deviate from those listed above because the STING technique is an operative intervention that requires the use of a general anesthetic and has potential risks. However, others advocate use of the STING technique in patients who would not normally be offered ureteroneocystostomy because the STING technique is minimally invasive and if successful may allow the patient to stop suppressive antibiotic therapy earlier and make multiple radiographic assessments unnecessary (5).

There are some situations in which application of the STING technique may be limited and other situations in which its use may be preferable to ureteroneocystostomy. Most large clinical series have excluded patients with major concurrent anatomic problems such as Hutch diverticulum, ureterocele, and bladder exstrophy (5). The rationale behind such exclusion is that the above listed conditions are associated with absolute lack of an intravesical tunnel, and the success of the STING

technique relies on augmentation of the intravesical tunnel. Patients with renal dysfunction and patients who are pregnant have generally also been excluded from treatment. Some reports have excluded patients with ureteral duplication (5) because earlier series had documented diminished cure rates of 50% (6). This is likely related to the difficulty of placing the implant accurately in the setting of a duplex configuration on the trigone. Collagen should not be used on patients with a positive skin test (3).

Use of the STING technique may have advantages over ureteroneocystostomy in patients who have a failed ureteric reimplant and reflux associated with a neurogenic bladder. Several series have documented salvage rates from 77 to 88% when patients with previous ureteric reimplantation failure were treated secondarily by STING (7,8). Such an intervention certainly causes less morbidity than reoperative ureteroneocystostomy and seems acceptable to both surgeon and patient (9). It should be noted that the STING technique may even be used to salvage a failed cross-trigonal reimplant. In this special circumstance, the ureteric orifice is injected at a right angle to its orientation (6). Surgeons who have performed ureteroneocystostomy on patients with neurogenic bladders realize the challenge of these procedures, especially in the setting of high-pressure bladders with thickened walls. Several studies of the STING technique have reported success in treating neurogenic reflux that is commensurate with that seen in nonneurogenic reflux, thus speaking to the application of this technique (10,11). It is imperative that the neurogenic bladder be concurrently managed with intermittent catheterization and/or anticholinergics to maximize the opportunity for cure.

STING TECHNIQUE

This procedure is usually performed as day surgery by giving the patient a general anesthetic. Cystoscopy is performed and an injection needle is advanced through the operating channel of the instrument to approach the 6 o'clock position of the ureteric orifice. The needle is then advanced for approx 5 mm in the plane between the bladder mucosa and muscle so that the needle rests under the posterior wall of the intravesical ureter. The implant is then injected until the ureteric orifice resembles an inverted crescent on a hillock and no gaping is seen (Fig. 1) (11a). The needle must remain in place for at least 30 s to prevent leak back of the injected material and is then removed. It is counterproductive to inject an orifice in more than one location; multiple needle punctures will potentially lead to leak back and subsequent failure. The volume injected depends on the severity of the defect at the ureterovesical junc-

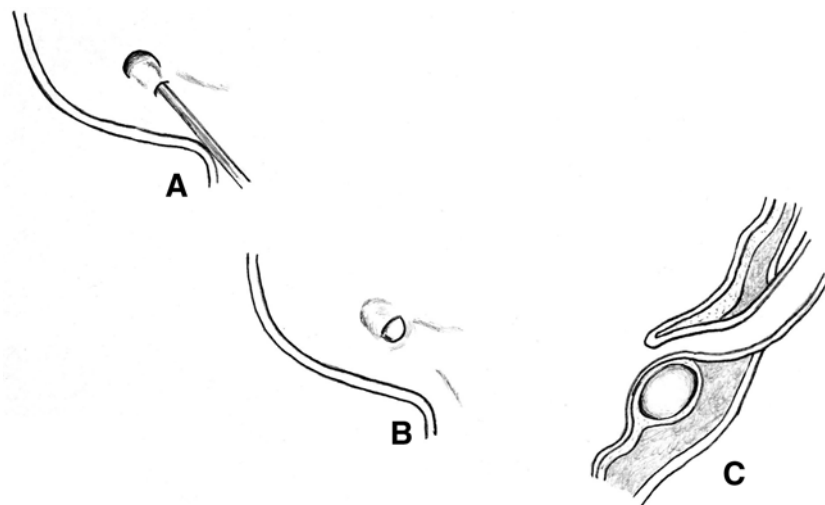


Fig. 1. (A) The endoscopic injection needle approaches the 6 o'clock position of the ureteric orifice and pierces the mucosa approx 4 mm distal to the orifice. The needle is then advanced for approx 5 mm in the plane between the ureter and the bladder muscle. (B) The implant is then injected until the ureteric orifice resembles an inverted crescent sitting on a hillock of the injected material. (C) The implant is seen in the ideal location within the submucosal space, producing coaptation of the ureteric orifice. (Reprinted with permission from ref. 11a.)

tion and the accuracy of needle placement, but generally ranges from 0.1 to 2.0 mL. The patient is sent home the same day and given antibiotic prophylaxis. A renal ultrasound is done 1 mo after the procedure, and a cystogram is done in 3 mo.

In general, the STING procedure is accomplished with minimal operative morbidity. There are infrequent reports of transient flank pain, hematuria, and UTI following STING procedures (7). However, in the majority of cases, complications are transient and easily managed. A more significant complication is that of ureteric obstruction caused by granuloma formation and fibrosis. This has been reported only with particulate materials such as Polytef, and in some cases has necessitated ureteroneocystostomy (12,13).

Although the STING technique is conceptually simple, there is a learning curve associated with its use. Dodat demonstrated this very well when he reported an initial failure rate of 40%, evolving to a respectable 8% over 4 yr (14). Thus, anyone undertaking this procedure

should work with a more experienced operator for their first few cases to rapidly climb the learning curve.

POLYTETRAFLUOROETHYLENE PASTE (POLYTEF OR TEFLON)

Teflon paste is noteworthy as being the first material used for the endoscopic treatment of VUR. Unfortunately, concerns about clinical safety in children has been a limiting factor in its widespread acceptance. Teflon has been used since the 1960s as a medical injectable in vocal chord augmentation (15) and subsequently was injected periurethrally for treatment of urinary incontinence (16). Matouschek first used Teflon paste for the application of subtrigonal injection in 1981 in an adult patient (1). Its use in children was initially described and popularized in 1984 by O'Donnell (17,18) who coined the term STING (2). This acronym has since come to refer to any subtrigonal injection procedure. Teflon for injection consists of a 1:1 suspension of polytetrafluoroethylene particles in glycerin. The resulting paste is quite viscous and requires injection by means of a pressurized gun system. The host quickly absorbs the glycerin and then Teflon initiates a foreign body granulomatous reaction, followed by fibrous encapsulation (2).

Both good initial cure rates and long-term durability have been reported with Teflon. As with all injectable materials, success rates are generally dependent on the initial grade of VUR and the number of injections administered. Initial cure rates have been reported as high as 94% following a single injection and up to 98% after a second injection in single systems with primary VUR (19). The majority of series in the literature document success rates averaging 80% after a single injection and 90% after a second injection (20–25). Long-term data suggest durability of an initial cure. At 1 yr posttreatment, maintenance of reflux-free status is reported in more than 92% of patients (18,21,23). A multicenter survey documented the long-term relapse of VUR in 11,510 cured renal units to be only 3% with a follow-up of 1 to 13 yr (26). Significant postoperative complication rates range from 0 to 1.5%, with complications including acute pyelonephritis and ureteric obstruction requiring reimplantation (19,22,24,27). Transient upper tract dilatation, which usually resolves by 1 mo posttreatment, may be observed in 20% of cases (22).

Concerns about safety have overshadowed the success and limited the widespread use of Teflon in North America. Teflon particles are small, ranging in size from 5 to 100 μm , with more than 90% of particles less than 40 μm . This small size would allow for migration resulting

from phagocytosis (17) and direct embolism into the venous circulation (28). Teflon particles within granulomata in lungs have been identified at autopsy in a patient treated with Teflon for urinary incontinence (29). The only case of documented migration of Teflon following STING procedure, which uses much lower volumes of Teflon than required to treat incontinence, was to a hypogastric ganglion in a patient whose injection was misdirected outside the bladder (17). Animal studies have shown that Teflon STING can result in migration to the lungs and brain (28). Whether this migration occurs clinically and could result in long-term sequelae in children remains unknown. The multicenter survey by Puri and Granata of 8300 children treated with Teflon STING and followed for up to 13 yr reported no clinically untoward effects resulting from the injection (26). The only possible adverse effect reported as a result of Teflon STING migration was a stroke that occurred 11 mo postinjection in a 6-yr-old girl with no other risk factors (30). Stroke is a rare pediatric event, and the cause is often unknown. However, it is possible that this represents an adverse event of Teflon embolization. In summary, although Teflon has not been proven harmful, there is enough suggestive evidence to question its safety. Its use, however, has established the STING procedure as a valid treatment modality for VUR and has spurred the search for equally efficacious and safer materials.

BOVINE DERMAL COLLAGEN

Cross-linked bovine dermal collagen has had wide application as an injectable for the STING procedure and for urinary incontinence. The material is prepared from solubilized and purified bovine collagen (35 mg/mL) to which 0.0075% glutaraldehyde is added to effect cross-linkage. Cross-linking serves to decrease implant degradation by collagenase and minimizes implant antigenicity (31). Cross-linked bovine collagen engenders minimal local tissue reaction, does not migrate distally, and is easily injected through a 25-gauge needle without the need for special instrumentation (32,33). It has been documented histologically in explants from patients in whom treatment failed that blood vessels grow into the collagen implants, allowing for the migration of fibroblasts and the laying down of autologous collagen (32). The first clinical series was reported from Johns Hopkins in 1991 and documented 1-yr posttreatment cure in 65% of renal units (59% of patients) after one to three injections (7). Subsequent reports from Europe documented cure rates of 60 to 70% of treated renal units 1–2 yr postinjection (34–36). It was observed that patients with higher grades of reflux, especially grade V, did not fare as well as those with low- to mid-grade reflux. These results are not on a par with cure by ureteroneocystostomy

but are within striking distance of those achieved with other injectables. None of the above quoted reports found significant patient morbidity from the use of collagen for the STING procedure. However, the two major obstacles to the wide acceptance of collagen for this indication are lack of long-term efficacy data and concerns regarding immunogenicity.

There are several published reports that allow critical examination of the long-term efficacy of the collagen STING technique. Reunanen followed 148 patients (197 renal units) for up to 4 yr posttreatment with radionuclide cystography after one to three STING procedures (37). The number of single-system renal units cured of grades III to IV reflux at 6 mo was 91.7%; at 2 yr, the cure rate was 85.3%; and at 4 yr, it was 81.8%, thus speaking to the reasonable durability of cure. De Grazia and Cimador also found moderate long-term efficacy among 93 children (129 renal units) treated by one or two collagen STING procedures (38). There was a 16.8% recurrence rate up to 7 yr after treatment. Other groups have had less gratifying long-term success, with reported cures of only 9% of 57 renal units at 17 mo postinjection (39). It should be noted that this latter report only offered one injection per patient and that improper implant placement or implant displacement by high bladder pressures may have negatively influenced the results (40). It is the opinion of these authors that collagen may be less durable than particulate injectables such as Teflon or Macroplastique, but in many instances, long-term persistence is achieved.

There have been concerns raised about the possibility of autoimmune disease incited by the use of injectable collagen (41). The first study to address this issue in pediatric patients after collagen STING documented that antbovine collagen antibodies developed in 30% of children at 13 to 24 mo after initial treatment. These antibodies did not cross-react with human type I or III collagen in any patient, nor did patients with positive titers demonstrate clinical features of autoimmune disease (42). A second study documented similar findings, with 22% of patients seroconverted to antbovine collagen antibodies within 6 to 8 mo after treatment and no clinical sequelae (43). The injected volume of collagen was not a determinant of immune status in either study. The take-home message from these studies is that injecting a patient with bovine collagen will result in a seroconversion rate of 20 to 30%, with production of antbovine collagen antibodies. It would seem prudent to skin test patients before and between injections to eliminate those who have become sensitized. There is no evidence that seroconversion leads to clinical expression of autoimmune disease. It would be advisable, however, to inform parents and patients of this issue and to follow patients over the long-term to ensure that no untoward sequelae of treatment ensue.

POLYDIMETHYLSILOXANE (MACROPLASTIQUE)

Polydimethylsiloxane STING has been used in Europe and is becoming more popular in Canada. The material comprises a solid silicone elastomer of heat-vulcanized polydimethylsiloxane suspended in a bio-excretable povidone gel. The elastomer form of silicone is much less likely to migrate than silicone gels or oils, such as those contained within silicone breast implants. Macroplastique is injected through a needle provided by the manufacturer. The needle must first be primed with a lubricant, and subsequently the polydimethylsiloxane is injected with a pressurized gun. The particle diameter of polydimethylsiloxane in this injectable varies from a mean maximum of 209 μm to a median minimum of 140 μm , with 76% of particles greater than 100 μm (44,45). It is felt that tissue macrophages or blood-borne monocytes cannot effect phagocytosis of a particle greater than 80 μm in diameter, and thus distal migration of such a large particle would not be possible. *In vitro* studies have documented that polydimethylsiloxane does not undergo phagocytosis by human macrophages or monocytes in tissue culture (44). Animal studies have documented that implants become encapsulated with fibrous tissue, elicit a chronic inflammatory reaction, comprising lymphocytes and foreign body giant cells, and serve as a scaffold for autologous collagen deposition by recruited host fibroblasts. Moreover, distal migration was uncommon, occurring in regional lymph nodes and the spleen in one of seven animals (46). It was felt that migration was caused by inappropriately deep injection into the bladder smooth muscle in this animal model. In contradistinction, two other groups found evidence of particle migration to lymph nodes, lung, kidney, and brain in dogs after subureteric or periurethral injection (47,48). The earliest clinical reports on the use of this material for STING emanated from Europe, where cure rates of 80 to 90% were reported after one injection (49,50). Shulman reported a cure rate of 90% among 114 children with grades II to IV VUR, some up to 2.5 yr after treatment (51). The only significant North American experience with this material has recently been reported from the Hospital for Sick Children in Toronto. Among a group of 74 children (112 renal units), reflux was corrected after one injection in 76% of children (81% of renal units), and a second injection cured 85% of children (90% of renal units) (8). As with other injectables, cure rates varied according to initial reflux grade. Voiding cystourethrogram (VCUG) was performed at 12 wk postinjection and only repeated if there was persistent reflux. Thus long-term efficacy data proven by VCUG at intervals after injection is not available. There were three patients in the Toronto series who underwent open ureteroneocys-

tostomy after polydimethylsiloxane injection. The explants demonstrated a surrounding fibrous capsule, with minimal surrounding inflammation, and there was no evidence of migration of the material to regional lymph nodes (8).

There is a paucity of long-term data on the efficacy of polydimethylsiloxane in the treatment of VUR. As mentioned earlier, Shulman's series showed some patients being cured as much as 2.5 yr after STING (51). In its role as a periurethral bulking agent for the treatment of urinary incontinence, the macroplastique injection procedure has resulted in cures up to 3 yr posttreatment (52,53). Clearly, the long-term follow-up of the children treated in Europe and Canada with polydimethylsiloxane STING will be important information to track. The issue of material safety has recently come to the forefront with a clinical report from France. In this paper, explants of Polytef or polydimethylsiloxane removed at the time of ureteroneocystostomy for STING failure were analyzed histologically. Fibrous encapsulation, chronic inflammation with foreign body giant cell reaction, and neovascularization of the implant were seen with both materials. However, it was felt that the explants of polydimethylsiloxane were associated with a more severe inflammatory reaction than Polytef. Furthermore, there was evidence that macrophages could fragment either material into 6- μ m particles, thus speaking to the potential for distant migration (54). Evidently, as with other injectable materials, ongoing surveillance of patient safety after polydimethylsiloxane STING will be required.

DEXTRANOMER IN SODIUM HYALURONAN (DEFLUX)

The Deflux system was developed in Sweden by Stenberg and Läckgren (55,56). Deflux consists of dextranomer microspheres, which form a network of cross-linked dextran, mixed 1:1 with high molecular-weight 1% sodium hyaluronan (NaHA) (55). Deflux easily injects through a fine needle. The technique is as described initially for the STING (56) with the exception that as the NaHA diffuses to the interstitium, overinjection may be required to achieve a satisfactory result (57). NaHA acts as a degradable carrier for the microspheres, disappearing within 2 wk of injection. The dextranomer microspheres degrade over time by hydrolysis but first initiate tissue augmentation by recruiting fibroblasts and other collagen-producing cells to the area (16). Animal studies show active ingrowth of fibroblasts and vessels and generation of collagen around the microspheres at 2 wk postimplantation, with a further increase in collagen at 3.5 mo. Twelve-month evaluation

of subcutaneous implantation in rats shows that implant size decreases to 77% of the initially injected volume. This is thought to be the result of hydrolysis of the microspheres (56).

Clinical experience with the use of Deflux in children began in 1993. Cure rates depend on the initial grade of VUR and the number of injections. Tekgöl (58) reported a 3-mo cure rate of 77% after a single injection for patients with initial reflux grades II and III, and Stenberg and Läckgren (56) reported a cure rate of 68% with grades III and IV reflux. The only long-term data available are provided by Läckgren et al (5). They reported that of 162 ureters cured at 3 mo, 8% had relapse of reflux greater than grade II. Persistence of reflux-free status was evaluated 2–5 yr posttreatment in 49 children, and 87% remained stable. Complications have been limited to transient dilatation of the upper tracts and UTIs, only one of which was an acute pyelonephritis (5,56,58–60). There have been no reports of significant ureteric obstruction requiring intervention.

There currently are no safety concerns regarding Deflux (5,61). Both of its components are biodegradable. NaHA lacks any immunogenic properties, (16) and cross-linkage of the dextran molecules prevents the circulation of free dextran, which might otherwise produce an anaphylactic reaction (5). The large size (80–120 μm) and spherical shape of the dextran particles prevent migration (16). Lack of early migration was shown in animal studies using radiolabeled dextranomer particles. DNA analysis of implant cells found no evidence of malignant transformation (55). Although success rates with Deflux do not reach those of the particulate injectables, the lack of safety concerns makes it attractive.

AUTOLOGOUS INJECTABLE MATERIALS

The quest for a safe injectable has naturally resulted in the investigation of various autologous tissues. The use of an autologous injectables avoids immunologic reactions and biocompatibility problems (17). Fat, blood, and chondrocytes have been clinically assessed for this application in humans. The evaluation of bladder smooth muscle cells and collagen have thus far been limited to animal studies and is discussed with the miscellaneous injectables.

AUTOLOGOUS FREE FAT

Autologous free fat grafts have been used extensively in cosmetic surgery. Their use in the endoscopic management of urinary incontinence has been tried and largely abandoned because of poor durability

of clinical effect (62). Their use in the management of VUR has been considered, but results have been less than satisfactory. Animal studies confirm that when autologous fat is injected submucosally in the bladder, only a relatively small fraction persists at 6 mo, regardless of the harvest site (62). Clinical results were reported in two select patient groups in 1994: adult candidates for renal transplant (63) and patients with spinal cord injury (64). Harvesting of the fat and STING took place under a single anesthetic. The fat was strained to allow for injection, and the STING was performed as initially described, except that volumes up to 10 mL were used. In the renal transplant group, only 1 of 13 refluxing ureters was cured at 3 mo, and a second injection had no effect (63). In the group with spinal cord injury, two of seven patients had a durable response at 6 mo (64). If autologous fat is to play a role in the future management of VUR, further modifications to improve both ease of handling and long-term durability would be required (65).

AUTOLOGOUS BLOOD

If proven effective, blood would have the advantage of being the most easily harvested autologous injectable. Khorl et al. in Japan initially reported some success in treating dogs with VUR in 1988 (66). The same group then reported their results in 13 adults with neuropathic bladders and reflux grades I–III (67). The technique varied from the usual in that a 5-Fr needle was used for injection and volumes up to 50 mL were injected (mean = 32 mL). After slow injection of the patient's heparinized blood, small amounts of thrombin and protamine were injected before removing the needle from the implant site. Short-term follow-up of 3 mo showed overall cure rates of 63% of ureters after a single injection. However, success was highest in ureters with grade I reflux (100%) and was only 33% in those with grade III reflux. No further data have been reported with this technique.

AUTOLOGOUS CHONDROCYTES

The basis for the concept of using autologous chondrocytes for STING was the observation that the mixing of harvested chondrocytes in alginate, a biodegradable polymer, resulted in cartilage formation (68). Investigations to assess this formulation for its suitability as a STING injectable have been performed in America since 1993 (68). Atala et al. successfully treated miniswine with surgically induced reflux by autologous cartilage STING, with cure lasting up to 6 mo (69). All implants showed evidence of cartilage formation at necropsy. The technique involves a two-stage surgical process, beginning with harvesting

auricular cartilage with the patient under a general anesthetic. The cartilage is then processed and the chondrocytes are grown *in vitro* for 6 wk. STING is then performed, with mixing of the chondrocyte-alginate gel with CaCl and CaSO₄ just before injection through a 5-Fr needle (70). Therefore, the safety benefits inherent to this autologous substance must be weighed against the need for an additional anesthetic. Caldamone and Diamond reported short- and long-term clinical success rates in 29 children (70). At 3 mo, reflux of grades III–V was cured in 55% of ureters after a single injection and in 83% after a second injection. At 1 yr, 70% of all injected ureters were cured (71). This success rate echoes that seen with bovine collagen. However, of concern was that patients who underwent open reimplantation after failed autologous chondrocyte STING showed no evidence of viable chondrocytes of the explants on histologic analysis. This has raised the question of whether the chondrocytes or the alginate vehicle alone plays a role in the successful STING group. Multicenter clinical trials are currently underway to answer this question, as are attempts to develop formulations that improve chondrocyte viability of the explants (71).

MISCELLANEOUS INJECTABLE MATERIALS

The STING armamentarium contains materials that have not yet found use in the clinical arena, despite their use in animal investigations.

Polyvinyl Alcohol Foam (Ivalon)

Polyvinyl alcohol foam (Ivalon) has found use as a skin substitute and an angiographic embolic agent and maintains its integrity and engenders minimal inflammatory reaction in these applications of the explants (72). Its use in the urinary tract was studied by Merguerian et al. in a rabbit model (45). After submucosal injection in the rabbit bladder, polyvinyl alcohol foam implants maintained their volume over 3 mo of study and were surrounded by a fibrous capsule with little inflammatory reaction. Moreover, there was no evidence of distant migration of the substance. However, concerns were raised because the material was noted to have a potential tumorigenic effect in animals, and thus its clinical use has been curtailed (73).

Bioglass

Bioglass is a glass ceramic compound that is biocompatible and binds to soft tissue (74). Bioglass particles may be suspended in sodium hyaluronate and injected through a 16-gauge needle. The material was studied in both rabbits and pigs by Walker et al., who documented

persistence of the implant over 3 mo with no distant migration of the particles (75).

The primary factor limiting its application for STING is delivery. Bioglass is viscous and cannot be injected through the small-gauge needles that are used in the STING technique. As a result, there has been no clinical experience with Bioglass in the treatment of reflux.

Silicone Balloon

A detachable, self-sealing silicone balloon has been developed as a novel approach to STING. The deflated balloon membrane is attached to a needle delivery system that is inserted into the subureteric space in the usual fashion. Once the balloon is in place, it is inflated with hydroxyethyl-methyl acrylate (HEMA) by means of a catheter that is integrated into the delivery system. The inflated balloon is then left in position as the catheter and needle are withdrawn. HEMA is a polymer that is biocompatible and nondegradable and has been used in contact lenses and hip prostheses (76). Atala et al. developed this technology and studied its application in animal models (77). They found that reflux was successfully treated in minipigs with the detachable balloon system. Moreover, the implants maintained their volume over time and did not engender local or distant granuloma formation. Although not yet approved for the STING, this system has been studied in a phase I clinical trial for the treatment of stress urinary incontinence. The results showed that the detachable balloons were safe and reasonably effective for this application (78). This system merits watching, as it may be applied to STING in the clinical context in the near future.

Autologous Collagen

Autologous collagen has been studied in the rabbit urinary tract. Collagen extracted from rabbit skin was radiolabeled and injected submucosally in the bladder of the same animal. The animals were subsequently killed, and the implants were found to be stable, maintaining their structural activity while engendering minimal local inflammatory reaction (79).

Bladder Smooth Muscle Cells

In addition to their study of autologous chondrocytes, Atala et al. have also investigated the use of autologous bladder smooth muscle cells suspended in alginate as an injectable for STING (80). Similar to results in animal experiments with autologous chondrocytes, the injected autologous smooth muscle cell suspension corrected reflux in minipigs

and maintained its integrity, with minimal local inflammation and no migration. Clinical trials with this material have yet to evolve.

As we look into the future, it is likely that the quest for the ideal injectable will continue. Developments in material science and tissue engineering will likely provide novel options for laboratory and clinical application.

COST ANALYSIS

One of the attractive aspects of the STING technique is its potential for reducing the costs of surgical care for patients with VUR. Two groups have examined its cost advantages over ureteroneocystostomy. It should be clearly stated that cost analysis does not factor in any measure of health benefit to the patient.

The first cost analysis of STING was based on the experience at one Canadian hospital with the use of collagen (3). In this study, only direct inpatient costs were accounted for. Thus, no provision was made for assessing the costs of outpatient visits and radiographic studies. Moreover, no measurement of indirect costs such as lost work time on the part of parents was taken into account. The costs were calculated in Canadian dollars (CDN), which currently trade for approx \$0.60 US dollars. The cost of treating one refluxing renal unit with a STING procedure was calculated to be \$1600 CDN compared with \$9100 CDN for ureteroneocystostomy. In this series, 29% of renal units required more than one injection for cure, and this added to direct costs. Furthermore, there was a 19% early failure rate and a 10% late failure rate that led to ureteroneocystostomy. All of these issues taken into account still allowed for a cost savings of \$4100 CDN per renal unit favoring STING over ureteroneocystostomy.

The second study was from Sweden and compared the costs of reflux management by antibiotic suppression for 3 to 6 yr, STING, and ureteroneocystostomy (4). Four hospitals were involved in the analysis of operative costs, and the materials used for STING were Polytef, Macroplastique, and Deflux. This study did include the cost of outpatient visits and radiographic assessments and estimated the indirect costs of lost work productivity on the part of parents. The costs were calculated in Swedish krona (SEK), which currently trade for approx \$0.10 US dollars. The authors ranked treatment strategies in the following order based on cost analysis: (1) STING 25,000–36,000 SEK, (2) antibiotic suppression 16,000–36,000 SEK, and (3) ureteroneocystostomy 65,000–95,000 SEK. The cost range accounts for unilateral and bilateral intervention in the surgical groups and either a 3- or 6-yr follow-up in the

medical group. The cost data for the STING cohort did take into account the occurrence of second injections and patients in whom STING failed and who then underwent ureteroneocystostomy. The authors were fully cognizant that the antibiotic prophylaxis and STING groups overlapped but were unable to account for the costs of breakthrough UTI and surgery in the medically managed group. However, it was clear that STING was the less expensive surgical option for their patients (4).

The above data suggest that STING is a less costly surgical intervention for reflux when compared with ureteroneocystostomy. However, several issues merit mention. First, costs vary a great deal according to the system of health care delivery, and this must be taken into account when assessing costs in a specific environment. Second, there has been a trend toward reducing hospital stay in patients who have undergone ureteroneocystostomy. In fact, a recent report found that patients were discharged within 24 h of surgery (81). The cost-analysis studies quoted above included longer hospital stays after ureteroneocystostomy, and thus newer concepts in delivery of care may make ureteroneocystostomy more cost competitive. Finally, the health benefits of either approach are not rolled into cost analysis, and thus the advantage of one technique over the other cannot be wholly assessed.

CONCLUSIONS

The STING concept has been applied for over two decades for the treatment of VUR. It has distinct advantages over traditional ureteroneocystostomy in terms of patient morbidity and treatment cost. Although the cure rate with this minimally invasive technique is approaching that of the “gold standard,” it is still not quite as effective as ureteroneocystostomy. The major stumbling block in the widespread acceptance of the STING procedure is the lack of an ideal material for injection. Currently available materials raise concerns regarding long-term durability, although the particulate injectables (Teflon and Macroplastique) go some way toward addressing this critique. The crux of acceptance of any material is its clinical safety, particularly when applied to children. All of the materials currently available, perhaps with the exception of Deflux and autologous chondrocytes, endure this stigma. The future will likely result in the development of safer exogenous materials and more effective autologous materials that will find application as injectables for STING. The concept of STING is sound, but the ideal injectable material remains a crusade for interested clinicians and scientists.

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5

Hypospadias

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INTRODUCTION

Hypospadias is the result of abnormal development of the penis that leaves the urethral meatus proximal to its normal glanular position anywhere along the penile shaft, scrotum, or perineum. A spectrum of abnormalities, including ventral curvature of the penis (chordee), a hooded incomplete prepuce, and an abortive corpora spongiosum are commonly associated with hypospadias.

Hypospadiology is a term coined by John W. Duckett Jr., the former chief of the Division of Urology at the Children's Hospital of Philadelphia (CHOP) and a pioneer in hypospadias repairs. Hypospadiology now encompasses a continuously evolving and expanding discipline. Although modern experiments have only recently begun to yield a deeper understanding of the genetic, hormonal, and environmental basis of hypospadias, the quest for a surgical procedure that consistently

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results in a straight penis with a normally placed glanular meatus has occupied surgeons for more than two centuries. Advances in understanding the cause of hypospadias and current approaches to correction of hypospadias to provide a cosmetically and functionally satisfactory repair are the focus of this chapter.

ETIOLOGY

Hypospadias results from partial or complete failure of urethral folds to form throughout their normal length, or from a failure of the folds to close distally if they have formed. The extent of the closure determines the position of the urethral orifice.

A unifying cause for hypospadias remains elusive and it is likely multifactorial. The hypospadiac anatomy appears consistent with incomplete embryologic development resulting from: (1) abnormal androgen production by the fetal testis, (2) limited androgen sensitivity in target tissues of the developing genitalia, or (3) premature cessation of androgenic stimulation caused by early atrophy of the Leydig cells of the testes (1).

Endocrine Factors

A number of writers have suggested that hypospadias represents a mild form of intersexuality. It could represent one end of a spectrum, the other of which is a completely feminized male (2). Hypospadias may result from an endocrinopathy in which there is a disruption in the synthetic biopathway of androgens. More than just a focal malformation, hypospadias may be a local manifestation of a systemic endocrinopathy. A qualitative androgen receptor abnormality or defects at a postreceptor level may explain the defect in some boys with hypospadias. For example, the blunted response to human chorionic gonadotropin (hCG) injections seen in many boys with hypospadias may suggest a mutation in the luteinizing hormone receptor in the testis or perhaps an increase in receptor numbers as a consequence of the previous stimulation (3). Of 15 boys 4 yr of age with severe hypospadias in a study by Allen and Griffin, 11 were diagnosed with a total of six distinct endocrine-related abnormalities (3). The most consistent finding was a subnormal testosterone response to hCG stimulation in seven boys. The authors postulated that this might represent a delay in maturation of the hypothalamic–pituitary–testicular axis.

Genetic Factors

Hypospadias is believed to have a complex genetic background, with gene expression acting in concert with environmental factors. The

familial rate of hypospadias is approx 7% and reflects a nonfamilial, sporadic finding in most cases. Recent studies have suggested a role for Müllerian inhibiting substance (MIS) in the cause of hypospadias. There is an inverse relationship between MIS and testosterone, which may be related to the MIS inhibition of cytochrome P450c17 CYP17, the enzyme that catalyzes the committed step in testosterone synthesis (4). Indeed, MIS may directly inhibit testosterone production by suppressing the CYP 17 gene (5). Abnormalities of other genes such as fibroblast growth factor 10 have also been shown to result in hypospadias (6).

Normal sexual differentiation depends on testosterone and its metabolites as well as on functional androgen receptors. Despite a correlation of certain clear defects in the androgen metabolism pathway and hypospadias, as in the 5 α -reductase defect (mutation in SRD5A2 gene on chromosome 2), such associations have been limited to few cases, underlining the importance of seeking other genetic explanations for this congenital defect (7).

Environmental Factors

The incidence of hypospadias has been on the rise worldwide. One possible explanation is environmental contamination. It is well known that insecticides, pharmaceutical drugs, and plant estrogens contain estrogenic ingredients, and that metal cans used in the canned food industry are coated internally with plastics known to contain estrogenic substances (6). These substances are ultimately present in fresh water and seawater in trace amounts that are bio-accumulated and concentrated in higher organisms of the food chain. For this reason, predators at the top of the food chain, such as large fish, birds, sea mammals, and humans accumulate high levels of estrogenic environmental contaminants. Thus, humans and wild animals are constantly exposed to estrogenic compounds known to disrupt reproduction, the so-called endocrine disrupters (6).

Maternal Factors

In 1967, Goldman and Bongiovanni suggested a role for maternal progestin exposure in the development of hypospadias (8). These researchers produced hypospadias in male rats by experimentally inducing congenital adrenal hyperplasia. A disturbance in the maternal–fetal hormonal milieu as a causative factor in humans was substantiated when male offspring conceived by *in vitro* fertilization requiring progestin therapy had a markedly increased incidence of hypospadias (9,10). Fredell and colleagues associated low birth weight with hypospadias in discordant monozygotic twins (11).

Future Areas of Research

Studies that elucidate the role of cellular signals other than testosterone and dihydrotestosterone in normal phallic development and hypospadias, endocrine disrupters, and mesenchymal-epithelial interaction may hold the key to explaining the cause of hypospadias (6). Research into the homeobox (Hox) gene may also open new avenues toward increased understanding of the cause of hypospadias.

EPIDEMIOLOGY

The incidence of hypospadias is rising and varies geographically. Prevalence ranges from 0.26 per 1000 births (both male and female births) in Mexico to 2.11 per 1000 births in Hungary, and 2.6 per 1000 live births in Scandinavia (12). A recent study found the rate of hypospadias in a 2-yr prospective study to be 38 per 10,000 live births in The Netherlands, a number six times higher than previously recorded (13). Sweet and colleagues reported a much lower incidence in Sweden of 1 in 1250 live male births (14).

In 1997, two independent surveillance systems in United States, the nationwide Birth Defects Monitoring Program (BDMP) and the Metropolitan Atlanta Congenital Defects Program (MACDP), reported that the rate of hypospadias had nearly doubled compared with immediately preceding decades (15). The incidence of all types of hypospadias increased from 20.2 to 39.7 per 10,000 live male births during the period from 1970 to 1993 (i.e., 1 in every 250 live male births was a boy with hypospadias, as measured by BDMP). MACDP reported a rise in severe hypospadias rate of between three- and fivefold. These rising trends, however, may simply reflect earlier diagnosis or an increase in reporting to registries of congenital defects. The increased reporting of more proximal than distal hypospadias cases, however, refutes the argument that these findings simply represent more frequent reporting of minor cases (16).

Recent studies have noted a rising rate of hypospadias in boys born prematurely and small for gestational age, boys with low birth weight, and boys born to mothers over 35 yr of age (17–19). Roberts and Lloyd noted an 8.5-fold increase in hypospadias in one of monozygotic male twins compared with single live male births (20). This may suggest a discrepancy in the supply of hCG to the fetus where single placenta is unable to meet the requirements of two developing male fetuses.

CHORDEE

Chordee is the ventral penile curvature that accompanies hypospadias in some cases. It is seen more commonly in severe cases of hypos-

padias but can also occur independent of hypospadias. Study of penile development by examination of fetal specimens has led to the understanding that chordee is a normal stage in penile development and that significant variation in the severity of chordee is noted at all stages of embryogenesis.

If chordee is indeed an arrest of normal embryologic development analogous to failure of descent of the testicle, it is no surprise that fibrosis is conspicuously absent in some clinical cases of chordee (21,22). This was further supported recently by Snodgrass et al., who found that all subepithelial biopsies of urethral plate examined under a microscope demonstrated well-vascularized connective tissue comprised of smooth muscle and collagen with no evidence of fibrous bands or dysplastic tissue (23). Baskin et al. found well-vascularized connective tissue under the epithelial surface of the urethral plate in a 33-wk fetus with distal hypospadias (24).

In some patients, chordee is present without hypospadias. Devine et al. described three types of chordee without hypospadias (25).

In class I, the most severe defect, the corpus spongiosum is deficient from the site at which the chordee begins up to the glans, and the urethra has a very thin tube of mucous membrane. In class II, the urethra has a normal corpus spongiosum with abnormal Buck's fascia and dartos fascia layers. In class III, only the dartos fascia layer is abnormal.

ASSOCIATED FINDINGS

Cryptorchidism and Inguinal Hernia

Between 8 and 10% of boys with hypospadias have a cryptorchid testicle, and 9 to 15% have an associated inguinal hernia (14,26,27). In boys with more proximal hypospadias, cryptorchidism may occur in as many as 32% (28). This strong association between proximal hypospadias and undescended testis further suggests that this clinical entity represents one end of a spectrum of endocrinopathy. The incidence of chromosomal anomaly in these groups of patients is much higher (22%) than the incidence of hypospadias (5–7%) or cryptorchidism (36%) occurring alone (29,30).

Intersexuality

Hypospadias and intersexuality are also believed to represent two ends of a spectrum (2). The more severe the hypospadias, the more likely an intersex state exists (31). Rajfer and Walsh reported intersexuality in 27.3% of boys with a normal-sized phallus, cryptorchidism, and hypospadias (32). Presence of severe hypospadias and nonpalpable tes-

tes with otherwise normal-looking phallus requires testing for an intersex state (31).

Partial androgen insensitivity, chromosomal abnormalities, Smith–Lemli–Opitz syndrome, 5 α -reductase deficiency, Drash syndrome, and others conditions can also occur in association with hypospadias.

Prostatic Utricle

The prostatic utricle is an elementary structure developing from the müllerian ducts cranially and from the wolffian ducts and the urogenital sinus caudally (33). Boys with hypospadias often have enlargement of the prostatic utricle, with resultant urinary tract infections, stone formation, pseudo-incontinence, and often, difficult catheterization (34–36). Devine et al. reported that 57% of patients with perineal hypospadias and 10% with penoscrotal hypospadias had prostatic utricle enlargement on urethroscopy (37). The overall incidence of utricle enlargement in patients with hypospadias was 14% in this series of 44 patients. Utricular enlargement in itself does not indicate an intersex state but is seen with increased frequency in patients with male pseudohermaphroditism.

PRESENTATION

The abnormal prepuce and ventral glans tilt of the newborn penis usually signifies the presence of hypospadias. Further examination of the penis typically reveals the proximally displaced urethral orifice that is often stenotic in appearance, but rarely obstructive. An exception is the megameatus variant of hypospadias. In this unusual case (6% of all distal hypospadias), an intact prepuce is present. The diagnosis is usually not made until after routine neonatal circumcision (38).

The anatomic location of the meatus and the extent of ventral curvature, or chordee, should be determined. In some instances, multiple pinpoint dimples may be present on the surface of the urethral plate as well as on the hypospadiac urethral meatus. The meatus is always the most proximal of these defects and can be confirmed by physical examination or with a probe. Meatal position may be classified as anterior (distal), middle, and posterior (proximal), with more anatomically specific subgroups being further applied (Fig. 1). The meatus is located on the glans or distal shaft of the penis in approx 70–80% of all boys who have hypospadias. The meatus is located in the middle of the shaft of the penis in 20–30% of boys who have hypospadias. Defects in the remainder of boys with hypospadias are more severe, with the urethral meatus located in the scrotum or even more proximally on the perineum (39).

The clinical association of hypospadias with intersex states occurred because of the increased understanding of the endocrinologic origins of

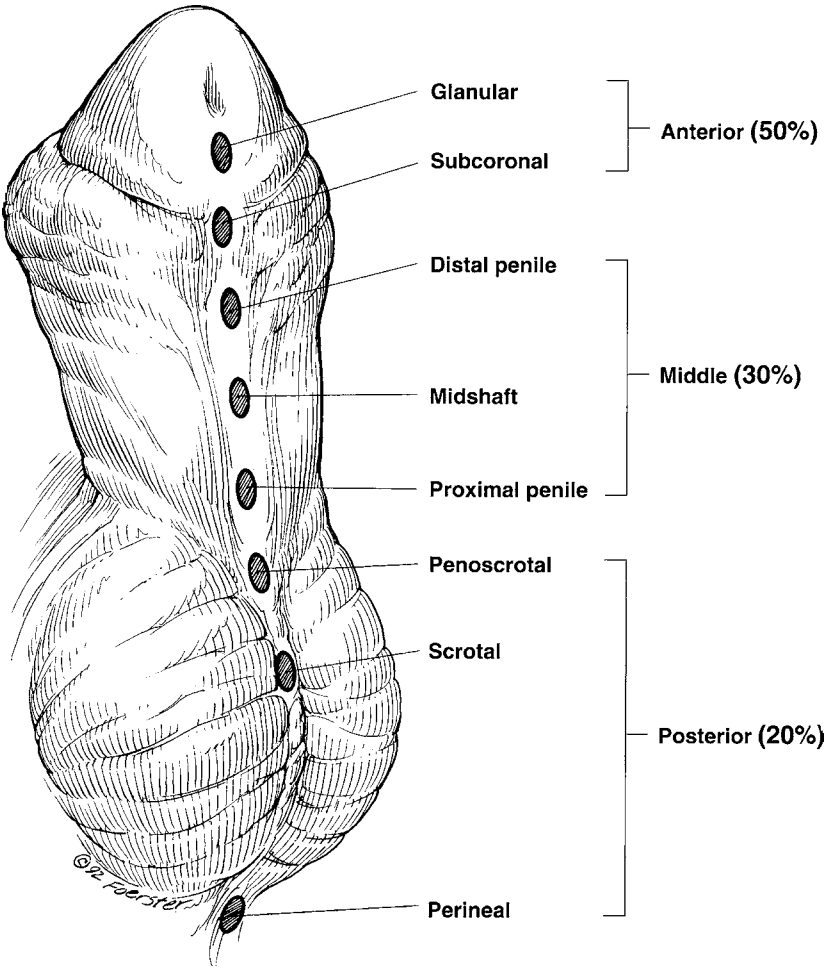


Fig. 1. Classification of hypospadias based on anatomic location of the urethral meatus. Anterior or distal hypospadias is the most commonly encountered variant. (From ref. 39a.)

hypospadias (32,40). Therefore, boys with severe proximal hypospadias and those with hypospadias and cryptorchidism should undergo karyotype analysis and intersex evaluation as indicated. The unilaterality or bilaterality of cryptorchidism concomitant with hypospadias does not predict the diagnosis of an intersex state.

A complete penile examination requires independent evaluation of penile length even as the diagnosis of hypospadias is confirmed. If the stretched penile length is significantly below the third percentile for

age, or if a clinical decision is made that inadequate phallic size would preclude adequate surgical repair of hypospadias, then pretreatment with androgen stimulation should be considered. Androgenic pretreatment with hCG has been shown to increase penile length and may also move the meatus to a relatively more distal position as the shaft elongates in response to the hCG (41).

SURGICAL REPAIR

The goal of hypospadias surgery is to create a functional sexual organ that is free of curvature. Equally important is the formation of a glanular urethral meatus that allows a boy to void with a laminar flow while standing. A cosmetically sound penis requires a cone-shaped glans and supple penile shaft skin.

Timing of Surgery

Experience over the past decade has confirmed the American Academy of Pediatrics statement that the ideal age for genital surgery is between 6 and 12 mo of age (42). This age range appears to insulate most children from the psychological, physiologic, and anesthetic trauma associated with hypospadias surgery. We prefer, however, to perform the repair at the age of 4 mo in boys with an adequately sized phallus and without medical problems. Healing seems to occur quickly, with fewer scars, and young infants overcome the stress of surgery more easily.

Instruments

The principles of plastic surgery are applicable to hypospadiology. Instruments such as fine scissors, 0.5-mm tooth forceps, and Castroviejo needle holders are commonly used with fine 6-0 or 7-0 absorbable sutures to handle tissue delicately and place sutures of adequate purchase precisely. Considerable variation exists among surgeons as to the choice of suture material. We prefer polyglycolic suture material for construction of the neourethra and for buried sutures and continue to use a glanular stay suture to minimize tissue handling during repair. Polydioxanone suture is not recommended for urethral repair because of its extended absorption time and increased urethral stricture rate (43).

Hemostasis

Adequate hemostasis may be achieved by a variety of techniques in hypospadias surgery. A tourniquet placed at the base of the penis that is removed every 15 to 30 min alone or combined with needlepoint spot and bipolar electrocoagulation are often used to control blood loss that

may occlude the surgical field. We avoid the use of electrocautery to minimize the potential for tissue damage caused by cautery dispersal and continue to inject 1:100000 epinephrine in 1% lidocaine along the proposed incision line. In our experience, this injection affords the twin benefits of adequate local hemostasis and hydrodissection of a reliable dissection plane between the skin and dartos fascia.

Dressing and Urinary Diversion

An ideal posthypospadias repair dressing should provide adequate but pliable compression and should be easily removable within 48 h in most cases. Numerous variations in type and style of dressing have been proposed, and even no dressing at all is a viable alternative for some (44,45). We prefer the “sandwich-type” dressing preferred by Duckett that compresses the penis against the lower abdominal wall by placing a Telfa pad and a folded gauze sponge on top of the penis followed by a bio-occlusive dressing (Tegaderm).

Urinary diversion is often preferred after proximal and midshaft hypospadias repairs, but its use in distal repairs is based on surgeon preference rather than on proven benefit. A multicenter experience reported by Hakim et al. revealed similar results for distal repairs with or without postoperative urethral diversion (46). We use a 6 Fr hydrophilic Kendall catheter placed through the neourethra and sutured to the glans, with a prolene suture anchored to the inner aspect of the meatus to avoid scarring of the glans. Because the rate of urinary infection is no different between an open and closed system, we allow the open end of the Kendall tube to passively drain into the outer of two diapers and prescribe chemoprophylaxis (47).

TYPES OF HYPOSPADIAS REPAIRS

A plethora of surgical options, from those representing truly novel approaches to modifications of known procedures, have been described for various presentations of hypospadias. The surgical technique that is most appropriate for a given case is heavily predicated on anatomic factors, previous surgical descriptions, and of course, a surgeon’s personal experience.

Historically, hypospadias repairs could readily be categorized as primary closures, meatal based flaps, dorsally based flaps, and free grafts. Conceptual advances such as recognition of the urethral plate and its potential for incision and preservation have profoundly affected the approach to hypospadias repair today. We describe, herein, the techniques we have implemented at our institution for hypospadias repair,

with an understanding that these descriptions are truly templates. In addition, these templates are constantly modified, amplified, and reinvented—a practice that is the very basis of evolution in hypospadiology.

Distal Hypospadias

MEATAL ADVANCEMENT, GLANULOPLASTY (MAGPI)

The MAGPI offers reliable cosmesis and long-term success when used for glanular and selected coronal meatus repairs. Urethral mobility, presence of a rounded glans, and the absence of significant chordee should be assessed to ensure an ideal outcome and avoid meatal regression. Urethral mobility can be adequately assessed by distal traction on the meatus with fine forceps.

The MAGPI begins with a circumferential incision 6–8 mm proximal to the corona of the glans and proximal to the meatus (Fig. 2A). Penile shaft skin is dissected in a “drop back” fashion, using extreme care ventrally over the corpus spongiosum to avoid urethral injury. Residual chordee or penile torsion may be corrected at this point. A longitudinal incision from the dorsal distal edge of meatus is carried to the distal glans groove as it transects the transverse bridge of tissue that is often present (Fig. 2B). The incised tissue edges are approximated in a Heineke-Mikulicz fashion, using 7-0 absorbable suture to effectively advance the meatus distally (Fig. 2C). The medial edge of the ventral meatus is then pulled distally, and the exposed glans edges are trimmed and anastomosed to leave the glans with a cosmetically sound, rounded appearance (Fig. 3C).

The dorsal hood foreskin is trimmed in the midline as Byar’s flaps allow adequate ventral skin transfer, and skin is approximated to the glans with absorbable, subcuticular suture to complete the repair (Fig. 4C).

TUBULARIZED, INCISED PLATE URETHROPLASTY (TIP)

Surgical repair of a hypospadias based on a flat urethral plate resulted in a horizontal, recessed meatus, and results were cosmetically superior when repairing a deeply grooved plate. This led Rich and colleagues to propose the “hinging of the urethral plate” by incising it distally (48).

Snodgrass extended this concept by incising the plate deeply through the entire urethral plate to the corporal bodies, followed by a Thiersch-

Fig. 2. (*opposite page*) Meatoplasty and glanuloplasty repair (MAGPI). (A) Circumferential incision 5 cm below the corona. (B) Transverse bridge of tissue distal to the meatus is sharply incised. (C) A Heineke-Mikulicz closure opens and advances the meatus. (D) Ventral meatal edge is pulled distally and

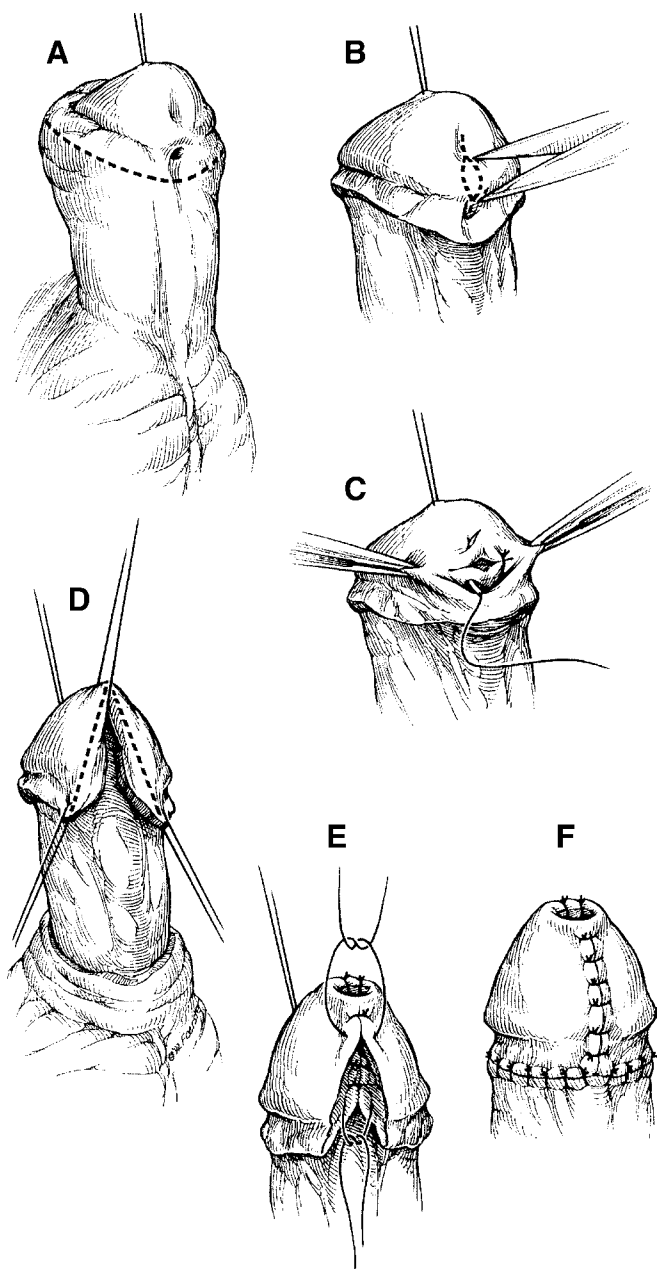


Fig. 2. (*continued*) the exposed glans edges are trimmed and approximated. (**E**) Glansplasty is performed with subepithelial sutures to leave a rounded, conical glans. (**F**) Dorsal skin is transferred ventrally, excess skin is excised, and no catheter is left in place. (From ref. 39a.)

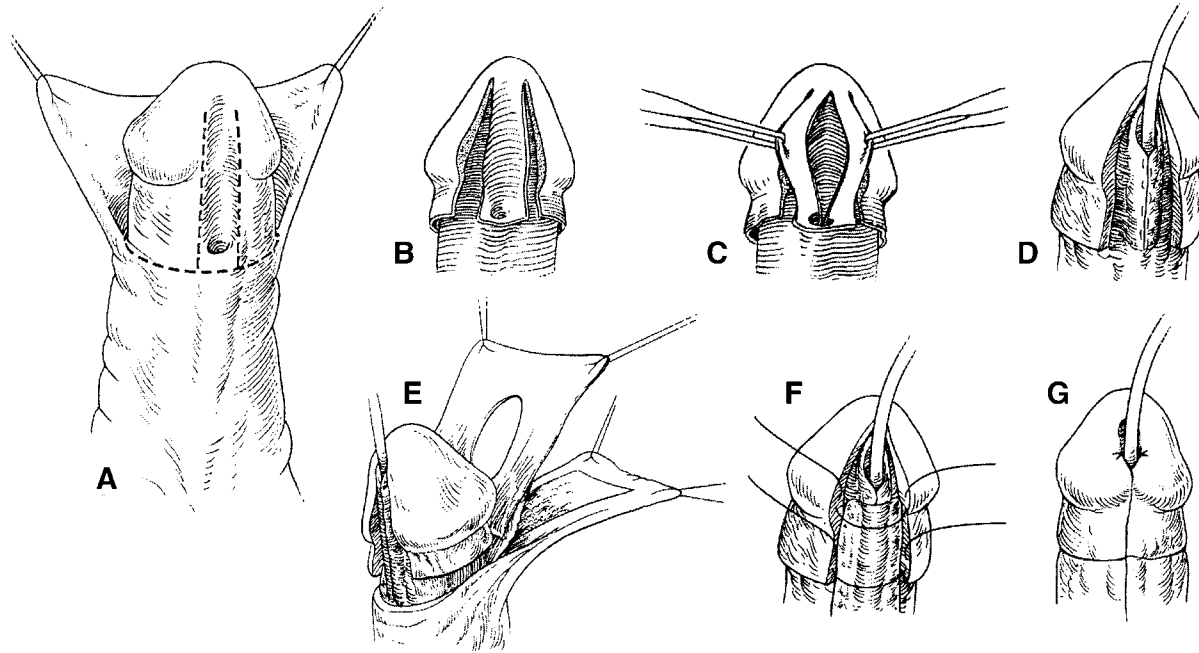


Fig. 3. Tubularized incised plate urethroplasty (TIP). (A) A circumscribing incision is made along dashed lines to deglove the penis. (B) The glans wings are mobilized laterally off the corpora cavernosa and separated from the urethral plate. (C) A longitudinal incision is made in the midline of the urethral plate to widen the urethral plate. (D) Tubularization of the urethral plate with a two-layer subepithelial approximation. (E) The dartos pedicle flap is dissected off the inner preputial skin and transposed ventrally to provide an additional cover over the suture line. (F) The glans wings are approximated in the midline with subepithelial sutures. (G) The meatus is sewn to the glans at two positions, and a urethral stent is secured in place. (From ref. 49.)

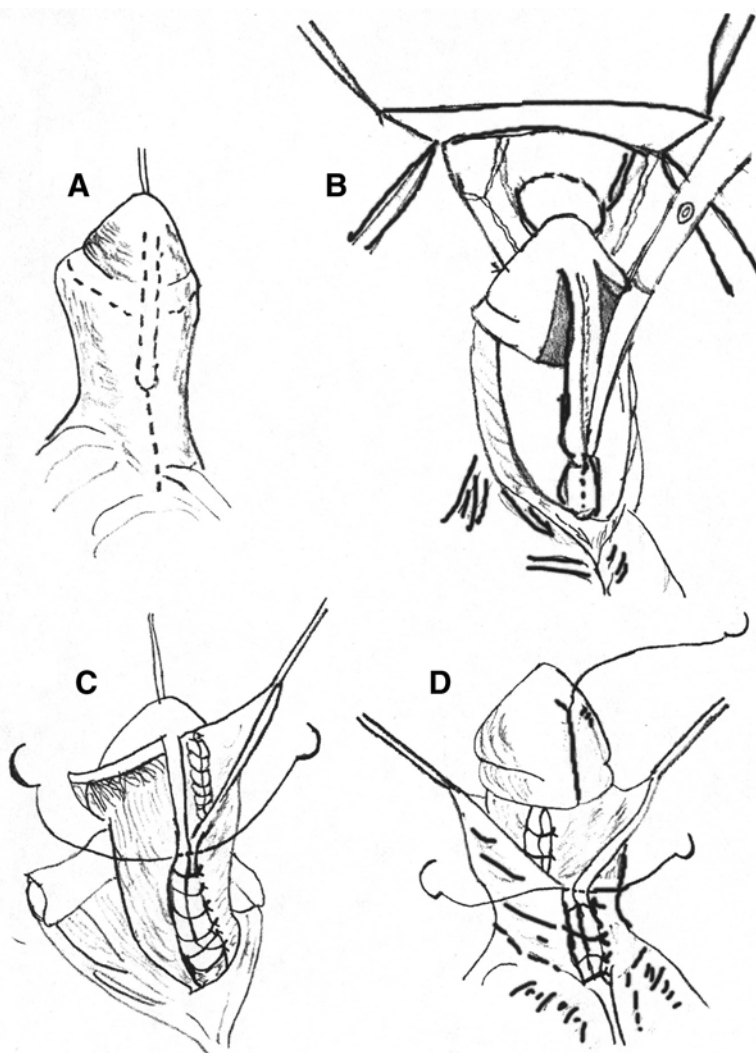


Fig. 4. Onlay island flap. (A) Dashed lines indicate initial circumcising incision carried along to the ventrum and anteriorly to provide a subcoronal collar (Firlit flap). Note that the midline incision is carried to the penoscrotal junction to facilitate adequate inspection of spongiosal tissue. (B) Penis is degloved and the native urethral meatus is incised back to normal spongiosal tissue. Thin, gossamer-like dysplastic urethral tissue is incised until normal, well-vascularized tissue is seen. Stay sutures separate the inner and outer faces of the preputial flap, and the onlay flap is mobilized with mesentery intact. A buttonhole in the mesentery allows ventral transposition without increasing torque on the penis. (C) The edges of the flap are sutured with subepithelial interrupted sutures. Tailoring of the flap minimizes the risk of diverticulum formation. (D) Byars flaps cover the skin-deficient ventrum with subcuticular sutures.

Duplay tubularization (50). Results of a multicenter trial supported the concept and TIP was applied to proximal hypospadias repairs (51,52).

A circumscribing skin incision is carried ventrally 1 to 2 mm proximal to the urethral meatus and followed by skin drop-back to the penoscrotal junction (Fig. 3A). Penile curvature is resolved and corrected by dorsal midline plication, if necessary. Two parallel longitudinal incisions in the glans allow lateral mobilization of the glans wings, taking care not to undermine the vascularity of the urethral plate (Fig. 3B).

The critical step in this repair involves a midline relaxing incision from within the meatus to the end of the urethral plate (Fig. 3C). The incidence of meatal stenosis is reduced by limiting the incision to the actual plate and not incising the rim of the glans at the distal margin of the plate (49). A 6-Fr stent is passed into the bladder and a two-layer, running subepithelial closure forms a tubular plate and creates a neourethra (Fig. 3D). Subepithelial 6-0 polyglactin sutures approximate the glans wings beginning at the corona to complete a glansplasty (Fig. 3F). The inherent disadvantage of superimposed suture lines with this closure may be countered by developing a dartos pedicle from dorsal shaft skin that is buttonholed and transposed to the ventrum (Fig. 3E).

In more proximal cases of hypospadias, TIP repair is done by first incising the proximal plate and leaving the distal plate intact. If the urethral plate increases in width, as expected, TIP is continued by incising the distal plate.

Middle and Proximal Hypospadias or Distal Hypospadias with Chordee

ISLAND ONLAY HYOSPADIAS REPAIR

Van Hook first introduced the concept of a preputial flap based on a vascular pedicle to repair proximal hypospadias in 1896 (53). Asopa and colleagues developed the technique for using inner preputial skin for a substitution urethroplasty, and Duckett furthered this technique with a transverse preputial island flap repair in 1980 (54,55). The island onlay flap evolved from the transverse preputial island flap as experience demonstrated that repair of the chordee with hypospadias could be accomplished by dissection of the subcutaneous tissue and dorsal midline plication, and that division of the urethral plate was required in only 10% of cases (56). The concept that spongiosum consists of vascularized tissue and smooth muscle bundles that may be used in hypospadias repair evolved in the 1980s after careful histologic examination (23,57). The onlay island flap is used for more than 90% of our patients who have subcoronal hypospadias.

The circumferential incision begins dorsally 6–8 mm proximal to the corona and is carried ventrally just proximal to the meatus (Fig. 4A). The incision is then carried further proximally to split ventral shaft skin in the midline to the penoscrotal junction (Fig. 4B). Parallel incisions 5-mm wide or narrower are then made along the urethral plate distally to the glans tip, at a point where the flat ventral surface of the glans begins to curve around the meatal groove. Care is taken to keep these incisions superficial to avoid injuring underlying spongiosum. The skin and dartos fascia are dropped back as residual chordee is released. When dissecting the skin, avoid entering the intrinsic vascularity of the skin to preserve its viability as a preputial flap. If dissection of the penile ventrum reveals thinned spongiosal tissue that is nearly transparent, as is commonly seen, we incise the urethra proximally to what appears to be normal spongiosum. The urethral plate need not be more than 2-mm wide before the onlay transfer.

The island onlay flap is outlined on the inner preputial skin surface with interrupted 5-0 polypropylene sutures that are also used as stay sutures (Fig. 4B). The sutures are grasped so that the fold of tissue between the inner and outer prepuce is accentuated. An 8- to 10-mm segment of this epithelium is sharply divided, with the initial incision made just beneath the skin at the junction between the inner and outer preputial faces of foreskin. The combined width of the preserved plate and the flap should be about 10 mm and should be no wider at the anastomosis than at the urethral meatus.

The freeing of the vascular pedicle begins at the midshaft, where it is most easily separated from the blood supply to the dorsal penile shaft skin. This approach to the harvest of the flap easily identifies the proper plane and assures preservation of blood supply to the flap. The splitting of ventral foreskin completed during the initial circumcising skin incision, in our experience, releases the base of the dorsal vascular pedicle and allows wider mobilization of preputial foreskin for flap isolation. The flap is then rotated ventrally, or more commonly, transferred by creating a window in the vascular mesentery through which the glans is passed, and then tapered proximally and distally (Fig. 4C). We have found that too wide a neourethra may lead to kinking or diverticulum formation. The appropriately designed flap is then sutured into place using lubricated interrupted 7-0 polyglactic suture at the proximal meatus and then in an interrupted subepithelial fashion along the lateral edges of the plate (Fig. 4C). We no longer close the flap over a feeding tube. We prefer to place the tube at the conclusion of the construction of the neourethra. The 8-Fr feeding tube then serves as a spacer to assure

an adequately sized glansplasty. The glansplasty is completed by medial rotation of mobilized glans wings, with 6-0 Maxon sutures placed parallel to the cut edge of the glans wing beginning at the urethral meatus (Fig. 4D). A 6-Fr Kendall urethral stent is placed, and the dorsal preputial skin is split in the midline and rotated ventrally to afford adequate circumferential skin coverage.

TRANSVERSE ISLAND TUBE REPAIR

The transverse island tube repair remains a preferred option at CHOP for proximal hypospadias cases amenable to a one-stage repair, even after division of the urethral plate to release persistent, severe penile curvature. This procedure incorporates inner preputial skin, as in the onlay technique, to be rolled completely into a neourethra without use of the urethral plate as a vascularized template. A bulky glansplasty, penile torque, and an oval rather than a slitlike meatal result have, however, hampered popular use of the island tube. Incorporating excessive preputial skin into a neourethra has also raised concern about forming a urethral diverticulum and turbulent flow. Our recent modifications to this classic procedure address these cosmetic and functional problems.

Skin incisions facilitate penile degloving to the penopubic junction dorsally and into the penoscrotal junction ventrally. The urethra is opened proximally to healthy vascularized spongiosum as in the onlay repair. The urethral plate is then transected at the corona and dissected off of the corporal tissue. An artificial erection delineates the extent of residual penile curvature, and a Heineke-Mikulicz incision made vertically and closed horizontally straightens the penis.

A segment of inner preputial tissue is harvested dorsally, as described for the island onlay. The pedicled flap is buttonholed and then ventrally transposed. Rather than rolling the tissue into a tube at this point, as previously described, we first anchor the medial margin of the flap to the urethra proximally (Fig. 5D). This maneuver allows the flap to be optimally tailored by stretching the skin to the opposite, anchored edge of the flap (Fig. 5D). The tube can be fashioned to align the anastomosis to the native urethra properly and to construct a tube of ideal caliber. A second interrupted suture line then rolls the tube effectively into the glans (Fig. 5E).

A glansplasty is completed with 6-0 Maxon sutures placed parallel to the cut edge of the glans as a horizontal mattress to cover the distal edge of the tube. A 6-Fr urethral stent is placed, and dorsal preputial skin is fashioned to provide adequate skin coverage, as in all hypospadias repairs.

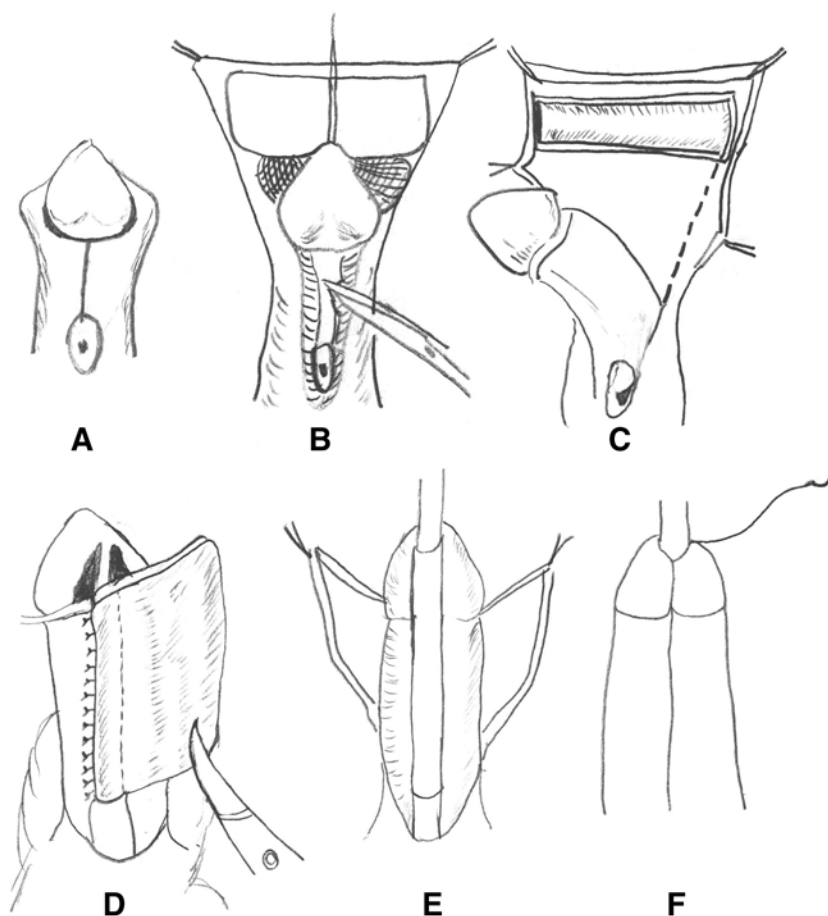


Fig. 5. Preputial island tube repair. **(A)** Incisions are made to facilitate degloving of the penis and circumscribing of the meatus. **(B)** The urethra is opened to a point where the spongiosum is no longer divergent. The urethral plate may be transected and dissected off of the corporal tissue. **(C)** An inner preputial skin flap is harvested dorsally. The preputial flap should be harvested beginning in the middle of the pedicle, and the mesentery should be preserved. **(D)** The medial margin of the flap is anchored to the urethra proximally. The remaining portion of the flap is anchored to the urethral plate with interrupted, subepithelial sutures. The flap is further tailored distally to roll the tube into the glans (dashed line indicates margin of urethral plate). **(E)** The glans is closed over an 8-Fr feeding tube. **(F)** Adequate skin coverage completes the repair with subcuticular sutures.

TWO-STAGE REPAIR

Occasionally we encounter challenging cases where severe chordee and a proximal meatus limit the applicability of a one-stage tube repair. In a few cases, injury to the vascular pedicle of the tube during harvest requires that the repair be staged.

Anecdotal and reported experience maintains, in fact, that the two-stage technique has fewer complications and better cosmetic results than the single-stage repair for select cases (58,59). In our anecdotal experience, however, the rate of fistula after the second stage of a two-stage repair is similar to that after a one-stage island onlay or tube repair.

A two-stage repair often involves a scrotoplasty with an aggressive attempt to relieve penile curvature, including transection and proximal removal of the plate. A dermal graft or tunica vaginalis may be interpositioned to bridge any defect in the ventral tunica albuginea surface, although this is rarely necessary in our experience.

Preputial skin at the dorsum is then split to rotate the resultant flaps ventrally. These flaps are allowed to settle into place and represent the future urethral plate.

The second stage is planned after an interval of about 6 mo. At that point, parallel vertical incisions 12–15 mm apart are mapped distally, beginning at the meatus and including the glans. Glans wings are mobilized, and the glans may be incised in the midline as with the TIP repair. Incisions are completed, and a neourethra is then tubularized to complete the repair using a standard Thiersch-Duplay technique. We aggressively cover the repair with dartos tissue or, in some cases, with processus vaginalis flaps taken adjacent to the spermatic cord on either side. In some cases, placement of the suture line into the scrotum facilitates healing. The penis is then mobilized from the scrotal flaps in a third stage, usually 3 to 12 mo later.

FREE GRAFTS

Severe proximal hypospadias and repeat hypospadias repairs may incorporate free grafts to construct a neourethra or to augment an existing plate. The versatility of most primary hypospadias repairs using preputial skin or the urethral plate, however, has obviated our use of free grafts for primary hypospadias repairs. At our institution, we reserve this technique for reoperations or for rare instances where a paucity of local tissue is evident (60). Free skin, bladder mucosa, tunica vaginalis, and buccal mucosa have variously been described as appropriate tissue for free graft use (61–63).

Our experience has been that bladder mucosa is less pliable than buccal mucosa, with the latter being less likely to shrink and requiring

a one-to-one ratio for harvest compared to the defect to be repaired. We prefer buccal mucosa because of its thick epithelium, tensile strength, and high levels of type-IV collagen, which favor graft take (64).

Use of bladder mucosa has been abandoned in favor of buccal for rare cases in which a free graft is required.

We prefer to harvest buccal mucosa from the inner cheek, taking care to avoid Stensen's duct. The graft is freed of adipose tissue and placed on a scaffold where it can be manipulated as necessary. The graft is trimmed to size if used as an onlay or tailored to be wrapped into a neourethra, without allowing for contracture in the case of buccal mucosa. Repairs completed with free grafts are stented for 10 to 21 d, depending on location and length.

Metro et al. and Hensle et al. have reported long-term results for buccal mucosal grafts in complex hypospadias reoperations (60,65). Overall complication rates between 32 and 57% were reported, with graft stricture and meatal stenosis being most common. All complications were evident by 11 mo postsurgery in both groups and were seen less commonly as the surgical experience widened. Buccal mucosa remains a viable nongenital tissue alternative for a select subgroup of patients requiring urethral reconstruction.

Complications

URETHROCUTANEOUS FISTULA

The postoperative appearance of a urethrocutaneous fistula is one of the most frustrating complications of hypospadias surgery, although it is increasingly rare. Adaptations in technique, including strict adherence to the principles of plastic surgery in tissue handling, avoidance of suture line overlap, and the transposition of additional tissue layers, have minimized the incidence of failure. The team at CHOP has previously reported a less than 5% fistula rate for the island onlay hypospadias repair technique (66).

When a fistula is diagnosed, whether as a perioperative or a delayed complication, at least 6 mo should elapse before surgery is repeated. This will allow inflammation and edema to resolve and will allow an accurate assessment of the viability and suitability of local tissue to be incorporated during reoperation. Whereas a small proximal fistula may be approached by excising the fistula tract to the urethra and performing an inverting closure with additional adjacent tissue, a larger fistula or multiple small fistulae often require a preputial- or dartos-based skin flap for an onlay closure. Transposition of considerable dorsal tissue to the ventrum during the first onlay repair will provide enough tissue for

a primary closure at reoperation. We have found that the smaller distal fistulae represent a deceptively more complex problem. Repair often requires an onlay to ensure adequate cover and reconstruction of the distal glansplasty.

URETHRAL DIVERTICULA AND MEATAL STENOSIS

Urethral diverticula may occur as an independent complication or as a secondary consequence of meatal stenosis. Incorporating excessive tissue in a primary closure or incomplete tailoring of an onlay flap increases the likelihood of diverticula formation. The diverticulum may be trimmed, followed by closure and overlay of local tissue. We prefer to wait up to 1 yr to repair diverticula after an onlay or tube repair because local revascularization of the flap during that interval allows for transection of the pedicle if required at the time of reoperation.

Urethral meatal stenosis occurs if blood supply to the distal urethra is compromised after hypospadias repair. Several technical modifications have sought to limit its occurrence. Limiting the involvement of the very distal urethral plate during a TIP or MAGPI procedure and avoiding an excessively tight glansplasty are now understood to be important measures to avoid meatal stenosis.

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6

Bladder Exstrophy for the General Urologist

New Discoveries and Modern Management

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and Fernando A. Ferrer, MD*

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REFERENCES

INTRODUCTION

In this chapter, modern techniques for managing the newborn with classic bladder exstrophy are discussed. Management is based on the author's experience and on data from more than 700 patients with the bladder exstrophy–epispadias–cloacal exstrophy spectrum seen at our institution. In addition, new basic science discoveries of interest to both the general and the pediatric urologist will be discussed. The primary objectives of modern surgical management of classic bladder exstrophy are as follows: (1) to create a secure abdominal closure, (2) to reconstruct a functional and cosmetically acceptable penis in the male and to

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reconstruct female external genitalia in the female, and (3) to preserve urinary continence, renal function, and volitional voiding. Currently, these objectives can best be achieved with newborn primary bladder and posterior urethral closure and early epispadias repair. Reconstruction of the bladder neck is undertaken when the bladder reaches an appropriate volume for an outlet procedure and the child is ready to participate in a postoperative voiding program. In this chapter, we will limit our discussion to the early management and initial primary closure of these infants.

INCIDENCE AND INHERITANCE

The incidence of bladder exstrophy has been estimated to be between 1 in 10,000 and 1 in 50,000 live births (1). However, data from the International Clearinghouse for Birth Defects monitoring system estimated the incidence to be 3.3 in 100,000 live births (2).

Two series have reported a 5:1 to 6:1 ratio of males to females born with exstrophy (1,2). The risk of recurrence of bladder exstrophy in a family is approx 1 in 100 (3).

Shapiro et al. determined that the risk of bladder exstrophy in the offspring of individuals with bladder exstrophy and epispadias is 1 in 70 live births, a 500-fold greater incidence than in the general population (3).

In a multinational review of exstrophy patients, Lancaster found two interesting trends: (1) bladder exstrophy tended to occur in infants of younger mothers, and (2) there was an increased risk at higher parity for bladder exstrophy but not for epispadias (2). Lately, several cases of bladder exstrophy have been seen with in vitro pregnancy (4).

EMBRYOLOGY

Bladder exstrophy, cloacal exstrophy, and epispadias are variants of the exstrophy–epispadias complex. The cause of this complex has been attributed to the failure of the cloacal membrane to be reinforced by ingrowth of mesoderm (5). Mesenchymal ingrowth between the ectodermal and endodermal layers of the cloacal membrane results in formation of the lower abdominal muscles and the pelvic bones. After mesenchymal ingrowth occurs, downward growth of the urorectal septum divides the cloaca into a bladder anteriorly and a rectum posteriorly. The paired genital tubercles migrate medially and fuse in the midline cephalad to the dorsal membrane before perforation. If the cloacal membrane is subject to premature rupture, its stage of development when membrane rupture occurs determines whether bladder exstrophy, cloacal exstrophy, or epispadias will result (6). Classic exstrophy occurs in 60% of those born with this complex. Of these, 30% are epispa-

dias variants, and 10% are cloacal exstrophies or minor variants, such as superior vesicle fissure, duplicate exstrophy, and pseudoexstrophy (7).

ANATOMIC CONSIDERATIONS

Exstrophy of the bladder is part of a spectrum of anomalies involving the urinary tract, genital tract, musculoskeletal system, and sometimes the intestinal tract. In classic bladder exstrophy, most anomalies are related to defects of the abdominal wall, bladder, genitalia, pelvic bones, rectum, and anus.

Bony Pelvis and Muscular Defects

Patients with classic bladder exstrophy have a characteristic widening of the pubic symphysis caused by malrotation of the innominate bones in relation to the sagittal plane of the body along both sacroiliac joints. In addition, there is outward rotation or eversion of the pubic rami at the junction with iliac bones. Recently, new data by Sponseller et al. using computed tomography (CT) of the pelvis with 3-D reconstruction has further characterized the bony defect associated with both classic bladder exstrophy and cloacal exstrophy (8). Sponseller et al. found that patients with classic bladder exstrophy had a mean external rotation of the posterior aspect of the pelvis of 12° on each side, retroversion of the acetabulum, and a mean 18° of external rotation of the anterior pelvis, along with a 30% shortening of the pubic rami (Fig. 1) These rotation deformities of the pelvic skeletal structures contribute to the short, pendular penis seen in patients with bladder exstrophy. Additionally, this rotation accounts for the increased distance between the hips, the waddling gait, and the outward rotation of the lower limbs seen in these children. These features cause little disability and usually correct to some degree over time.

A recent study using 3-D CT has further increased our understanding of the pelvic anatomy in patients with bladder exstrophy. Stec et al. showed that the iliac wing angle in these patients was 11.4° larger than in controls, the sacroiliac joint was 9.9° more externally rotated, and the pelvis was rotated 14.7° in the superoinferior plane (Fig. 2) (9). Thus, this study revealed that the sacroiliac joints were more externally oriented than previously thought and the pelvis was rotated inferiorly, a previously unknown observation. These findings should improve our understanding and our surgical approach to pelvic osteotomy in these patients.

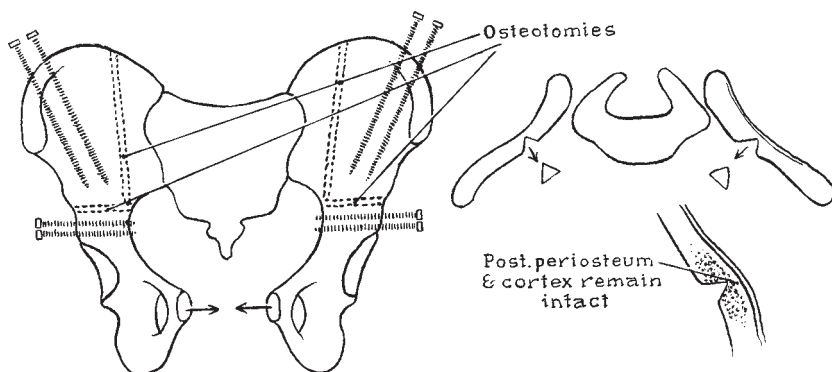


Fig. 1. Bony deficit in the pelvis of classic bladder exstrophy. The difference between normal anatomy and that of classic bladder exstrophy is illustrated. The posterior pelvic segment is externally rotated to a mean of 12° on each side, but the length is not different. The anterior pelvic segment is externally rotated 18° (6° more than the posterior segment) and is shortened by a mean of 30%. The distance between the triradial cartilage is increased by 131%.

Using modern 3-DCT reconstructions of the pelvis in newborns, Stec et al., for the first time, found marked defects in the pelvic floor (10). The puborectalis and levator complex was found to be asymmetric in its support and attachment to the pelvic floor (Fig. 3). Only 30% of the muscle bulk was found anterior to the rectum supporting the bladder neck and anterior pelvic structures; 70% was posterior to the rectum. There is a 50/50 distribution in normal, age-matched controls. This factor clearly plays a role not only in the biomechanics of continence but also in pelvic floor support in the female.

Abdominal Wall Defects

The triangular defect caused by the premature rupture of the abnormal cloacal membrane is occupied by the exstrophied bladder and the posterior urethra. The fascial defect is limited inferiorly by the intrasymphyseal band, which represents the divergent urogenital diaphragm. This band connects the bladder neck and posterior urethra to the pubic ramus on anatomic study. The anterior sheath of the rectus muscles has a fanlike extension behind the urethra and bladder neck that inserts into the intrasymphyseal band. At the upper end of the triangular fascial defect is the umbilicus. In bladder exstrophy, the distance between the umbilicus and the anus is always foreshortened. Although an umbilical hernia is usually present, it is usually of insignificant size. The umbilical hernia is repaired at the time of the abdominal wall clo-

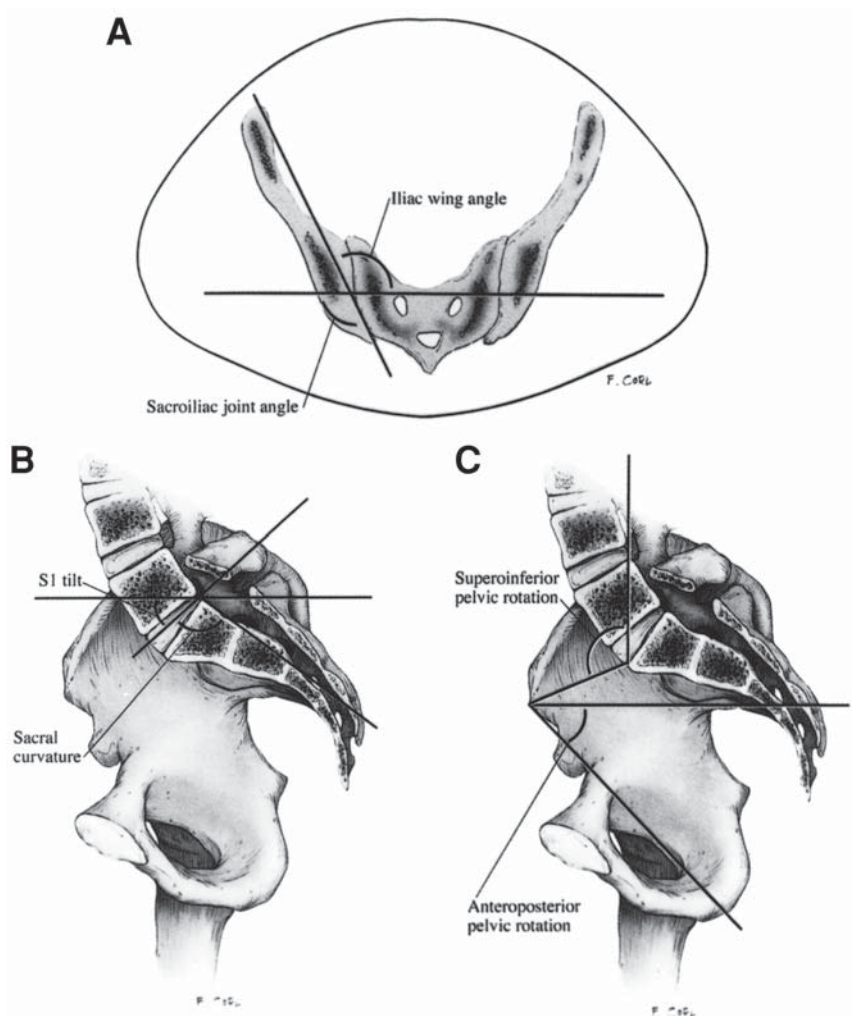


Fig. 2. (A) Iliac wing angle and sacroiliac joint angle. The mean iliac wing angle was 11.4° larger (138° vs 126.6°) in children with bladder exstrophy than in controls. The sacroiliac joint angle was 9.9° larger in children with exstrophy (128.8°) than in controls (110.9°). The mean sacroiliac joint was rotated 9.9° more toward the coronal plane in patients with classic exstrophy than in controls. (B) The sacroiliac joint tilt and sacral curvature. The sacroiliac joint tilt was 29.9° in children with exstrophy and 34.7° in controls. No difference was found in the sacral curvature between the exstrophy sacrum (95°) and the normal sacrum (93.3°). (C) Superoinferior pelvic rotation and anteroposterior pelvic rotation. In patients with exstrophy, the pelvis was rotated significantly more inferiorly than in controls. The superoinferior rotation angle in children with exstrophy was 140.4° vs a mean angle of 125.7° in controls, a difference of 14.7° . The mean angle of the anteroposterior pelvic rotation was similar in children with exstrophy (55°) and controls (52.3°), indicating no meaningful deviation from normal.

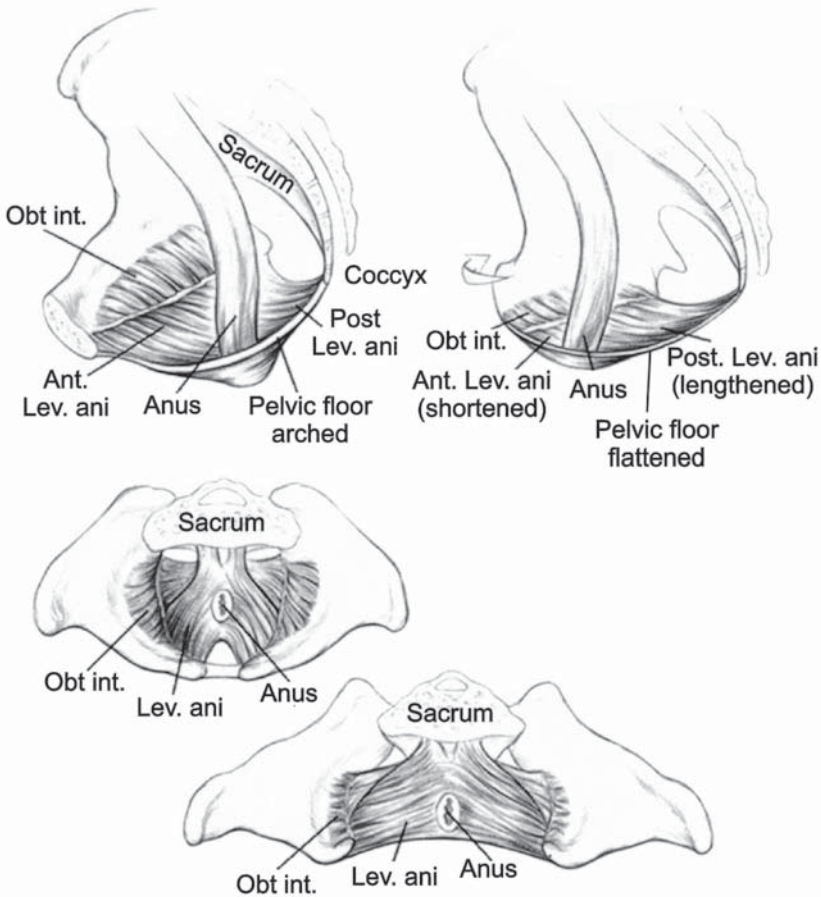


Fig. 3. The muscular defect in bladder exstrophy. These figures demonstrate that, in children with exstrophy, 70% of the major pelvic floor muscles are distributed posterior to the rectum rather than being equally distributed posterior and anterior. This is seen quite easily in the bottom of the figure in the coronal plane.

sure. Connely et al., in a review of 181 children with bladder exstrophy, reported inguinal hernias in 81.8% of boys and 10.5% of girls (11).

Anorectal Defects

The perineum is short and broad, with the anus situated directly behind the urogenital diaphragm. The perineum is displaced anteriorly, corresponding to the posterior limit of the triangular fascial defect.

The divergent levator ani and puborectalis muscles and the distorted anatomy of the external sphincter result in varying degrees of anal incontinence and rectal prolapse. Anal continence is usually imperfect at an early age but typically improves. Prolapse virtually always disappears after bladder closure or cystectomy and urinary diversion.

Male Genital Defects

The male genital defect is severe and is the most troublesome aspect of the surgical reconstruction, independent of the decision to treat by modern staged closure, combined closure, or by some form of urinary diversion. Formerly it was thought that individual corpus cavernosum were of normal caliber but appeared shorter because of the wide separation of the crural attachments, the prominent dorsal chordee, and the shortened urethral groove. However, a recent paper by Silver et al. has described the genital defect in bladder exstrophy in much greater detail (12). Using magnetic resonance imaging, adult men with bladder exstrophy were studied and compared with age- and race-matched controls. The authors found that the anterior corporal length in male patients with bladder exstrophy was almost 50% shorter and 3% wider than that of normal controls (Fig. 4). A functional and cosmetically pleasing penis can be achieved when the dorsal chordee is released, the urethral groove is lengthened, and the penis is somewhat lengthened by mobilizing the crura in the midline. Patients with a very small or dystrophic penis should be considered for sex reassignment only after consultation with other physicians and exhaustive counseling of parents regarding the implications of this step. Potency is preserved in almost all exstrophy patients. Testis function has not been studied in a large group of postpubertal exstrophy patients, but it is generally believed that fertility is not impaired by testicular dysfunction.

Female Genital Defects

Reconstruction of the female genitalia presents a less complex problem than reconstruction of the male. The vagina is shorter than normal, slightly greater than 6 cm in depth, but of normal caliber. The vaginal orifice is frequently stenotic and displaced anteriorly; the clitoris is bifid, and the labia, mons pubis, and clitoris are divergent. The uterus enters the vagina superiorly so that the cervix is in the anterior vaginal wall. The fallopian tubes and ovaries are normal. Female patients are typically able to bear children, but most require Caesarian section to prevent damage to their inadequate pelvic floor.

Urinary Defects

At birth, the bladder mucosa may appear normal; however, ectopic bowel mucosa, an isolated bowel loop, or more commonly, a hamar-

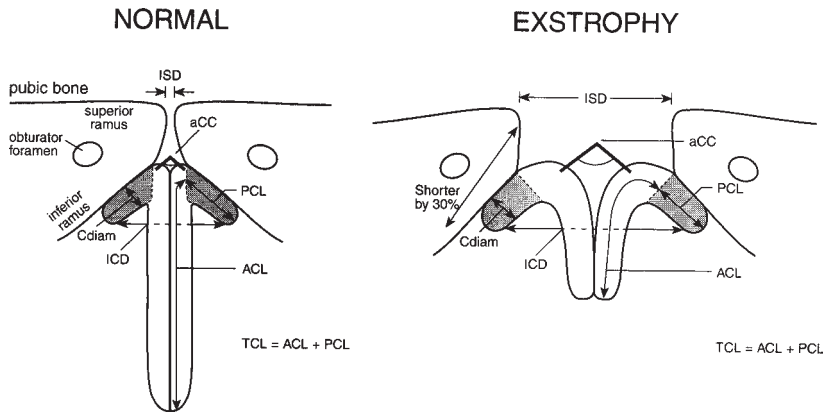


Fig. 4. The urogenital defect in patients with bladder exstrophy. The penile and pelvic measurements in normal men and in patients with exstrophy. ACC, corpora cavernosus tendon angle; ACL, anterior corporal length; Cdiam, corpus cavernosus diameters; ICD, intracorporal distance; ISD, intrasymphyseal distance; PCL, posterocorporal length; TCL, total corporal length.

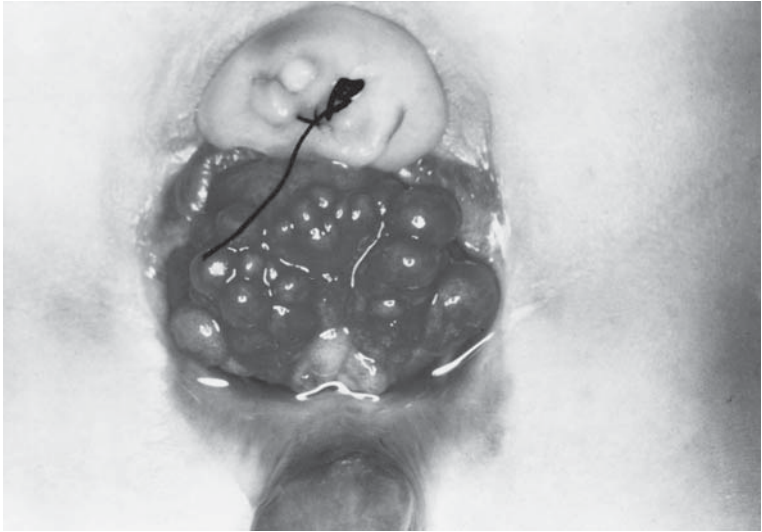


Fig. 5. Small newborn male exstrophy unsuitable for closure. Notice small size of bladder template and hemartomatous polyps covering the surface of the bladder.

tomatous polyp may be seen on the bladder surface. The size, distensibility, and neuromuscular function of the exstrophied bladder, as well as the size of the triangular fascial defect to which the bladder muscles

attach, affects the decision to attempt repair. When the bladder is small, fibrosed, inelastic, and covered with polyps, functional repair may be impossible (Fig. 5). The more normal bladder may be invaginated or may bulge through a small fascial defect, indicating the potential for satisfactory capacity after successful initial closure (Fig. 6A,B). The true defect cannot be adequately evaluated until it can be examined with the patient anesthetized, because bladders that appear small in the nursery may have a good bit of bladder sequestered below the fascial defect.

The upper urinary tract is usually normal, but anomalous development does occur. Horseshoe kidney, pelvic kidney, hypoplastic kidney, solitary kidney, and dysplasia with megaureter are seen in these patients. The ureters have an abnormal course in their termination. The peritoneal pouch of Douglas between the bladder and the rectum is enlarged and is usually deep, forcing the ureter down laterally in its course across the true pelvis. The distal segment of the ureter approaches the bladder from a point inferior and lateral to the orifice, and it enters the bladder with little or no obliquity. Therefore, reflux in the closed exstrophy bladder occurs in 100% of cases, and subsequent surgery is usually required at the time of bladder neck reconstruction.

PRENATAL DIAGNOSIS AND MANAGEMENT

Recent reports have indicated that it is possible to diagnose bladder exstrophy prenatally. The absence of a normal fluid-filled bladder on repeat examination suggested the diagnosis, as did a mass of echogenic tissue on the lower abdominal wall. A study of 25 prenatal ultrasound examinations of newborns later diagnosed with classic bladder exstrophy made several observations. The review found that there was absence of bladder filling, patients had a low-set umbilicus, there was widening of the pubic ramus, the genitalia were small, and there was a lower abdominal mass that increased in size as the pregnancy progressed and as the intra-abdominal viscera increased in size (13). These were the key factors in several pregnancies summarized in retrospect (14,15).

Prenatal diagnosis of bladder exstrophy allows for optimal prenatal management, including delivery in a pediatric center and appropriate prenatal counseling of the parents.

DELIVERY ROOM AND NURSERY

At birth, the bladder mucosa is usually smooth, pink, and intact; it is also sensitive and easily denuded. In the delivery room, the umbilical cord should be tied with 2-0 silk close to the abdominal wall so that the umbilical clamp does not traumatize the bladder mucosa and cause



Fig. 6. (A) Nice-sized bladder template and penis in newborn male with exstrophy. (B) Female exstrophy. Note bifid clitoris and anterior location of vagina.

excoriation of the bladder surface. The bladder may be covered with a nonadherent film of plastic wrap to prevent the mucosa from sticking to clothing or diapers. In addition, each time the diaper is changed, the plastic wrap should be removed, the bladder surface should be irrigated with sterile saline, and a new square of plastic wrap should be placed.

The parents should be educated by a surgeon who is experienced in managing patients with bladder exstrophy. An exstrophy support team should be available and should include a pediatric orthopedic surgeon, pediatric anesthesiologists, social workers, nurses with special interests in bladder exstrophy, and a child psychiatrist with experience and expertise in treating children with genital anomalies. It is important to note that the need for changing the sex of rearing in patients with classic bladder exstrophy is almost nonexistent in the male child.

Cardiopulmonary and general physical assessment can be carried out in the first few hours of life. Ultrasound studies can provide evidence of renal structure and drainage, even in the first few hours of life before the patient undergoes closure of the exstrophy defect. A thorough neonatal assessment may have to be deferred until the child can be transported to a major children's medical center. In these days of modern transportation, no child should be more than a few hours away from a neonatal center with full diagnostic and consultative services. During travel, the bladder should be protected by a plastic membrane to prevent damage to the delicate newborn bladder mucosa.

Occasionally, it may become evident before surgery that a small fibrotic bladder patch stretched between the edges of a small triangular fascial defect without elasticity or contractility cannot be selected for the usual closure procedure. Examination with the patient under anesthesia may at times be required to assess the bladder adequately, particularly if there is considerable edema, excoriation, and polyp formation between birth and the time of assessment. Decisions regarding the suitability of bladder closure and timing of surgery should be made by surgeons with a great deal of experience in the bladder exstrophy condition. In a recent review by Dodson et al. at one institution, an initial judgment that the bladder was too small for closure was made in 20 patients (15). When the bladder had grown sufficiently, closure was undertaken. Long-term follow-up revealed that 50% achieved a bladder capacity for bladder neck reconstruction and, of those, 50% are dry after bladder neck reconstruction, and 50% required other adjunctive procedures.

PRIMARY BLADDER CLOSURE

Over the past two decades, modifications in the management of functional bladder closure have contributed to a dramatic increase in the

success of the procedure. The most significant changes in the management of bladder exstrophy are the use of early closure of the bladder, posterior urethra, and abdominal wall, usually by pelvic osteotomy; the early repair of epispadias; the reconstruction of a competent bladder neck and reimplantation of the ureters; and most importantly, the definition of strict criteria for the selection of patients suitable for this approach. The primary objective in functional closure is to convert the bladder exstrophy into complete epispadias with incontinence, with balanced posterior outlet resistance that preserves renal function but stimulates bladder growth. Typically, epispadias repair is now performed when the patient is between 6 and 12 mo of age, after testosterone stimulation. Bladder neck repair usually occurs when the child is 4 to 5 yr of age, has an adequate bladder capacity (85 mL minimum), and most importantly, is ready to participate in a postoperative voiding program.

Pelvic Osteotomy

Pelvic osteotomy performed at the time of closure confers several advantages, including easy re-approximation of the symphysis, with diminished tension on the abdominal wall closure, eliminating the need for fascial flaps; placement of the urethra deep within the pelvic ring, enhancing bladder outlet resistance; and movement of the large pelvic floor muscles near the midline, where they can support the bladder neck and aid in eventual urinary control. After pubic approximation with osteotomy, some patients are able to stop and start the urinary stream, experience dry intervals, and in some cases, become completely continent. Of patients referred to our institution because of failed exstrophy surgery, most of those with partial or complete dehiscence of the bladder or with major bladder prolapse had not undergone prior osteotomy at the time of initial bladder closure (17).

We recommend using bilateral transverse innominate and vertical iliac osteotomy when bladder closure is performed more than 72 h after birth (18). In addition, if the pelvis is not malleable or if the pubic bones are greater than 4 cm apart at the time of initial examination with the patient under anesthesia, osteotomy should be performed, even if closed before 72 h of age. A well-coordinated surgery and anesthesia team can perform osteotomy and proceed to bladder closure without undue loss of blood or risk of prolonged anesthesia in the child. However, one must realize that osteotomy, posterior urethral and bladder closure, along with abdominal wall closure, are 5- to 7-hr procedures in these infants.

Combined osteotomy is performed by placing the patient in a supine position, preparing and draping the lower body below the costal margins, and placing soft, absorbent gauze over the exposed bladder. The

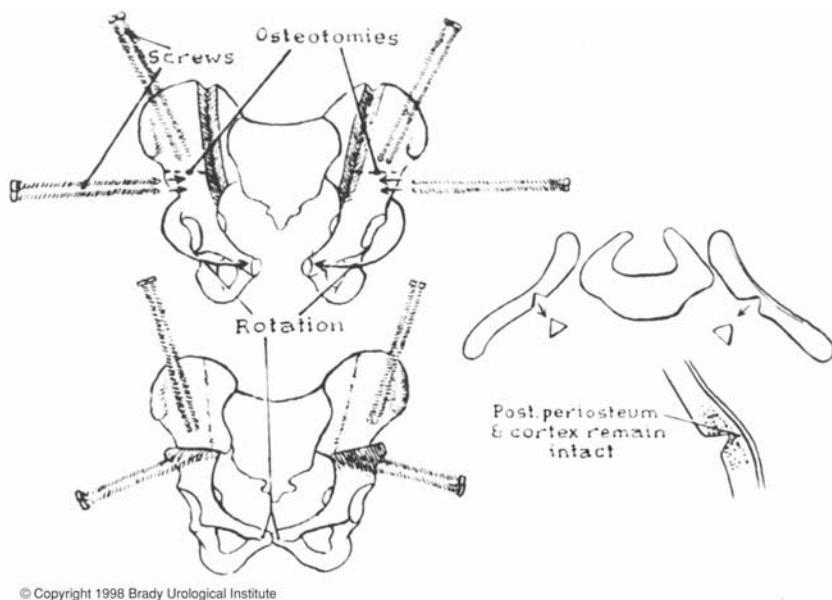


Fig. 7. Combined transverse and anterior innominate osteotomy and anterior vertical iliac osteotomy, with pin placement and preservation of the posterior periosteum and cortex.

pelvis is exposed from the iliac wings inferiorly to the pectineal tubercle and posteriorly to the sacroiliac joints. The periosteum and sciatic notch are carefully elevated, and a Gigli saw is used to create a transverse innominate osteotomy exiting anteriorly at a point halfway between the anterosuperior and anteroinferior spines. This osteotomy is created at a slightly more cranial level than that described for a Salter osteotomy to allow placement of external fixator pins in the distal segments (Fig. 7).

In addition to the transverse osteotomy, incision of the posterior ileum, using the anterior approach, may correct the deformity more completely. This is important because anatomic studies have shown that the posterior portion of the pelvis is also externally rotated in patients with exstrophy, and that as patients age they lose the elasticity of their sacroiliac ligaments. For this part of the procedure, an osteotome is used to create a closing wedge osteotomy vertically and just lateral to the sacroiliac joint (Fig. 7). The proximal posterior iliac cortex is kept intact and is used as a hinge. Using this combination of osteotomies, abnormalities in both the anterior and posterior aspects of the pelvis can be easily corrected (19).

Two fixator pins are placed in the inferior osteotomized segment, and two pins are placed in the wing of ileum superiorly. Pin placement is

confirmed by radiographs, soft tissues are closed, and the urologic procedure is performed. At the end of the procedure, external fixators are applied between the pins to hold the pelvis in a corrected position. Light longitudinal skin traction is used to keep the legs still. The patient remains supine in traction for approx 4 wk to prevent dislodgement of tubes and destabilization of the pelvis (Fig. 8). The external fixator is kept on for approx 6 wk until adequate callous is seen at the site of the osteotomy. Newborns who undergo closure without osteotomy in the first 48 to 72 h of life are immobilized after surgery in modified Bryant's traction in a position in which the hips have 90° of flexion. Modified Bryant's traction should be maintained for 4 wk (Fig. 9).

Bladder, Posterior Urethra, and Abdominal Wall Closure

The various steps in primary bladder closure are illustrated in Fig. 10A–K. A strip of mucosa 2 cm wide, extending from the distal trigone to below the verumontanum in the male and to the vaginal orifice in the female, is outlined for prostatic and posterior urethral reconstruction in the male and adequate urethral closure in the female. The male urethral groove length is typically adequate, and no transverse incision of the urethral plate needs be made for urethral lengthening. If the groove is too short for adequate posterior urethral closure, judicious use of paraexstrophy flaps is indicated. The diagrams in Fig. 10B–D show marking of the incision with a blue pen from just above the umbilicus down around the junction of the bladder and the paraexstrophy skin to the level of the urethral plate. The appropriate plane is entered just above the umbilicus, and a plane is established between the rectus fascia and the bladder. The umbilical vessels are doubly ligated and incised and allowed to fall into the pelvis. The peritoneum is taken off the dome of the bladder at this point so that the bladder can be placed deeply into the pelvis at the time of closure. The plane is continued caudally between the bladder and the rectus fascia until the urogenital diaphragm fibers are encountered bilaterally. The pubis will be encountered at this juncture. A double-pronged skin hook can be inserted in the bone at this time and pulled laterally to accentuate the urogenital diaphragm fibers and help the surgeon incise these fibers between the bladder neck, posterior urethra, and pubic bone. Gentle traction on the glans of the penis at this point will show the insertion of the corporal body on the lateral inferior aspect of the pubis. These urogenital diaphragm fibers are taken down sharply with electrocautery to the pelvic floor in their entirety. If this maneuver is not performed adequately, the posterior urethra and bladder will not be placed deeply into the pelvis. As a result, when the pubic bones are brought



Fig. 8. Modified Buck's traction along with external fixating device used in 18-mo-old with prior failed exstrophy closure.

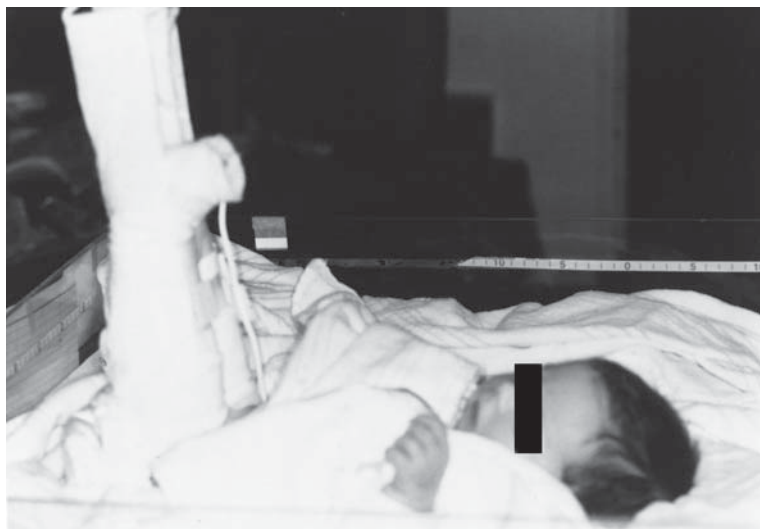


Fig. 9. Modified Bryant's traction in newborn with bladder exstrophy not requiring osteotomy.

together, the posterior vesicourethral unit will be brought anteriorly and will be in an unsatisfactory position for lateral reconstruction.

The corporal bodies are not brought together at this juncture. Cantwell-Ransley epispadias repair performed later will require that the

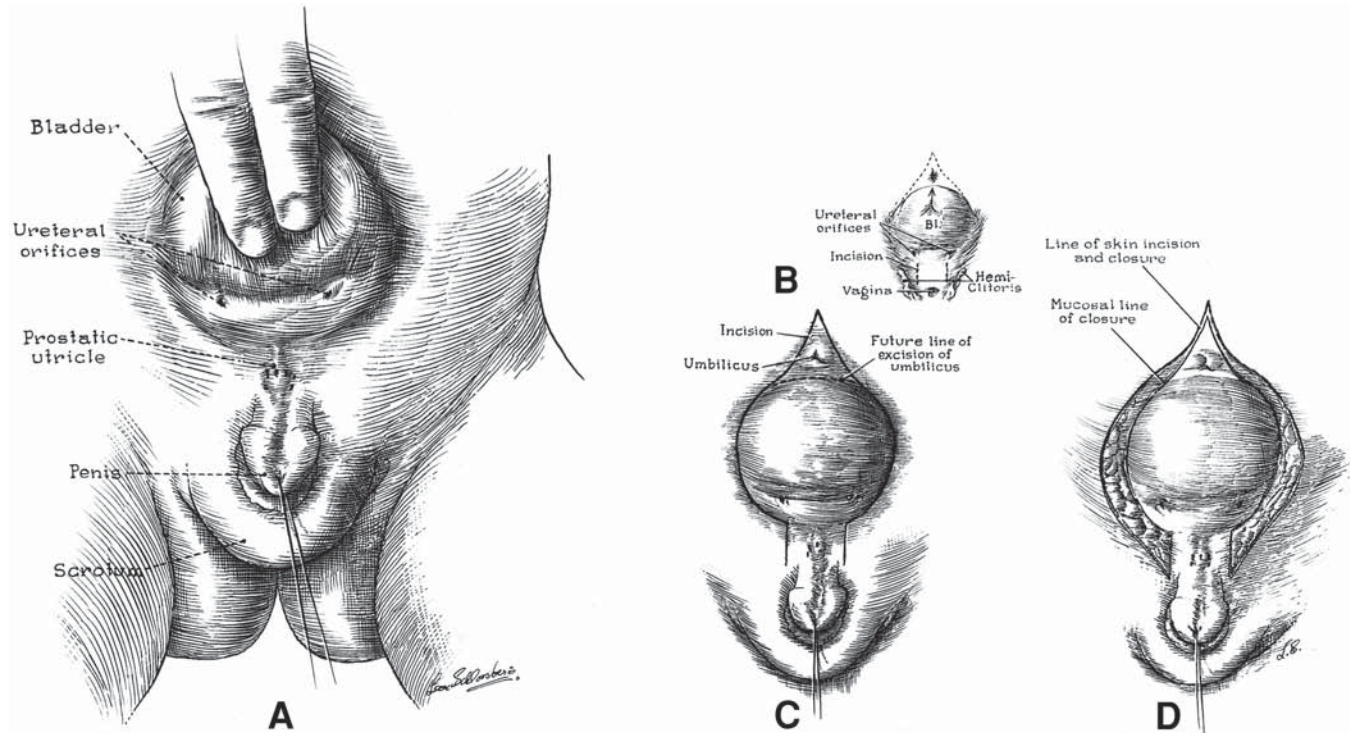


Fig. 10. Steps in the primary closure of the posterior urethra and bladder and proximal abdomen, with or without osteotomy, in the newborn with exstrophy. (A–D) The incision line around the umbilicus down to the urethral plate. If the urethral groove is adequate, no incisions are made in the urethral plate at the time of initial closure. Note that in the inner aspect of the labia minora in the female patient (B), the clitoral halves are denuded to allow complete reconstruction of the external genitalia along with the bladder (BL) and urethral closure.

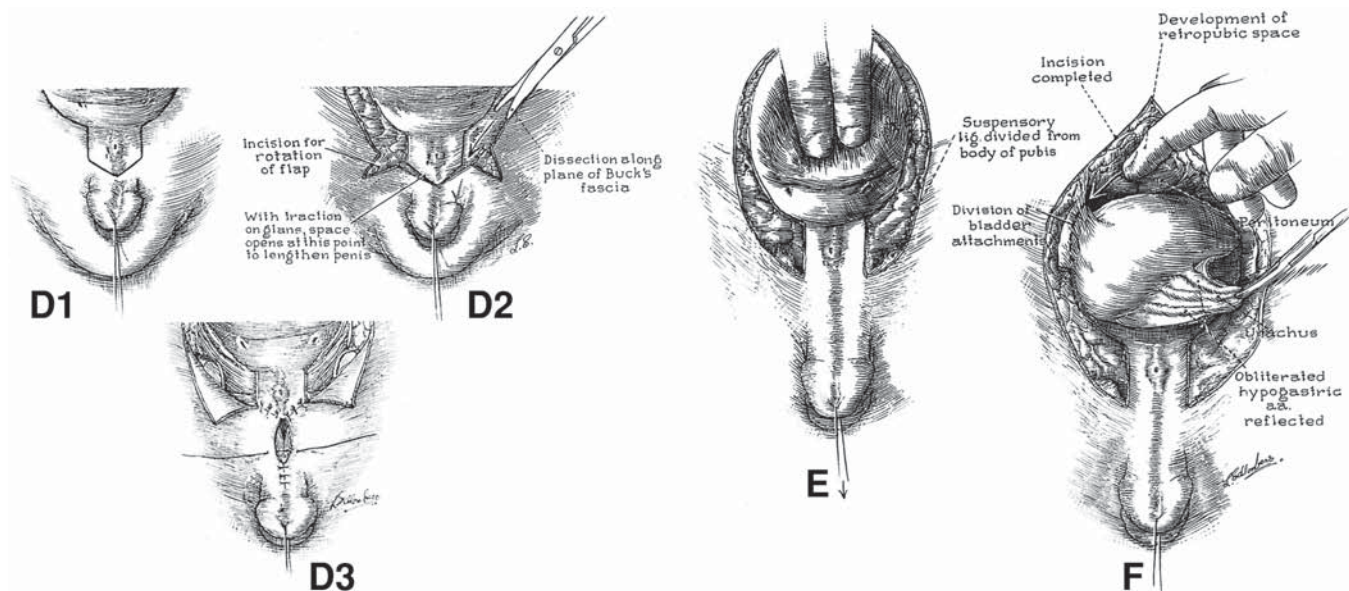


Fig. 10. (D1–D3) The incision across the urethral plate uses rotation flaps in case urethral lengthening must be done at the time of initial closure. (E–F) Development of the retropubic space from below the area of the umbilical insertion to facilitate separation of the bladder from the rectus sheath and muscle.

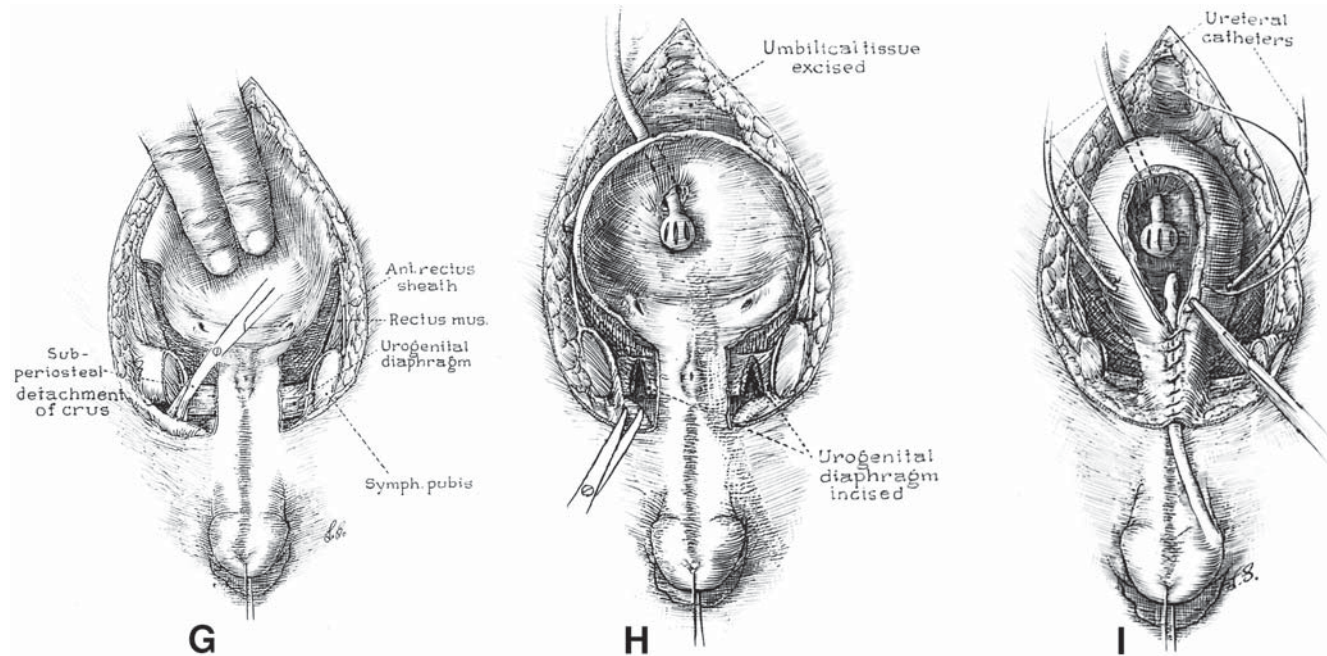


Fig. 10. (G) Medial extension of the rectal muscle attaching behind the prostate to the upper border of the urogenital diaphragm. The urogenital diaphragm and anterior corpus are freed from the pubis in a subperiosteal plane. (H) Final incision deep into the remnant fibers of the urogenital diaphragm down to the level of the levator muscles and placement of a suprapubic cystostomy tube. (I) Exit of ureteral stents from the lateral sidewall of the bladder and the first layer of bladder closure.

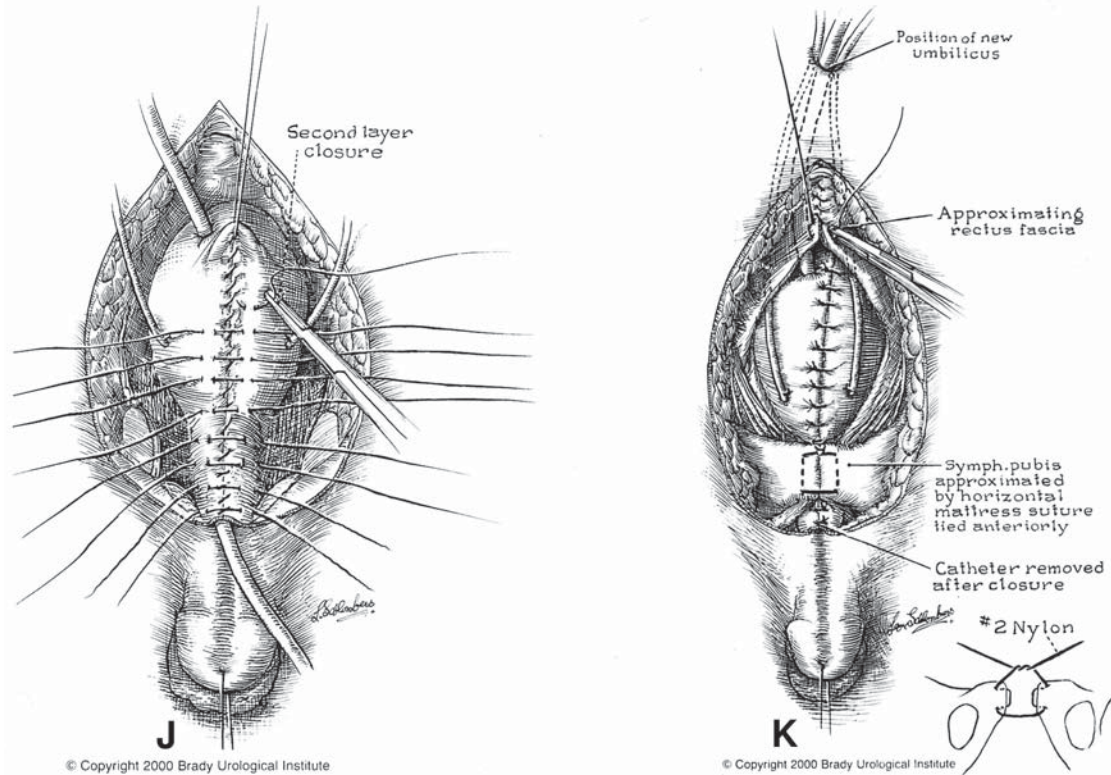


Fig. 10. (J) Second layer of the bladder wall closure. **(K)** Horizontal mattress suture tied on the external surface of the pubic symphysis as an assist in the medial rotation of the greater trochanters. Suprapubic tube and ureteral stents are brought out cephalad to the bladder at the site of the neoumbilical opening. (Drawings by Leon Schlossburg, 2000, Brady Urological Institute).

urethral plate be brought beneath the corporal bodies. If the urethral plate is left in continuity, it must be mobilized to the level of the prostate to create as much additional urethral and penile length as possible. Further urethral lengthening can be done at the time of epispadias repair, when the patient is around 6 mo of age.

Apparent penile lengthening is achieved by exposing the corpora cavernosa bilaterally and freeing the corpora from its attachment to the suspensory ligaments on the anterior part of the inferior pubic rami. However, Silver et al. showed that patients with exstrophy have a 50% shortage of length in the corporal bodies compared with normal controls, and therefore, any penile lengthening is more correction of chordee and change in angulation of the penis rather than true penile lengthening.

After incision, the wide band of fibers and muscular tissue representing the urogenital diaphragm is detached subperiostally from the pubis bilaterally. Reluctance to free the bladder neck and urethral well from the inferior ramus of the pubis causes the neobladder opening to move cephalad if any separation of the pubis occurs during healing. The mucosa and muscle of the bladder and the posterior urethra well onto the penis are then closed in the midline anteriorly. This orifice should accommodate a 12-Fr to 14-Fr sound comfortably.

The size of the opening should allow enough resistance to aid in bladder adaption and prevent prolapse but not enough outlet resistance to cause upper tract changes. The posterior urethra and bladder neck are buttressed to the second layer of local tissue if possible. The bladder is drained by a suprapubic nonlatex Malecot catheter for 4 wk. The urethra is not stented to avoid necrosis and accumulation of secretions in the neourethra. Ureteral stents provide drainage during the first 14 d after closure, when swelling caused by the pressure of closing a small bladder may obstruct the ureters and cause obstruction and transient hypertension. If there are no problems with the stents during healing, we leave the stents in for as long as 2 to 3 wk.

When the bladder and urethra have been closed and the drainage tube placed, pressure over the greater trochanters bilaterally allows the pubic bones to be approximated in the midline. Horizontal No. 2 mattress sutures are placed in the pubis and tied with a knot away from the neourethra. In a good closure, we are able to use another stitch of No. 2 nylon at the most caudal insertion of the rectus fascia onto the pubic bone. This adds to the security of the pubic closure. A V-shaped flap of abdominal skin at a point corresponding to the normal position of the umbilicus is tacked down to the abdominal fascia, and the drainage tubes exit this orifice. The method described by Hanna is the procedure that we use most commonly (20). Before and during the procedure,

the patient is given broad-spectrum antibiotics in an attempt to convert a contaminated field into a clean surgical wound. Nonreactive sutures of polyglycolic acid (Dexon/Vicryl) and nylon are used to avoid an undesirable stitch reaction or stitch abscesses.

Combined Bladder Closure and Epispadias Repair

The staged closure of bladder exstrophy has yielded consistently good cosmetic and functional results, and the use of osteotomy has improved the potential for successful initial closure and later continence. In an effort to decrease costs, to decrease the morbidity associated with multiple operative procedures, and possibly to effect continence, there has been recent interest in performing single-stage reconstruction or in combining procedures for appropriately selected patients. Use of single-stage reconstruction was first described by Jeffs and Gearhart in 1991 for failed exstrophy closures (21). With the addition of the recent report by Grady and Mitchell, who studied newborns, we now have results from groups of boys who underwent single-stage reconstruction (bladder closure and epispadias repair) in infancy (22). We believe that this technique should be limited to older infants (> 6 mo) because of recent experimental evidence indicating that newborn bladders differ from those of older infants in level of maturity of muscle and connective tissue components. In addition, the senior author has seen severe complications in patients who had “complete” repair when the procedure was done by a surgeon who was not experienced in exstrophy surgery.

These patients should be carefully selected, especially newborns, for the above reasons. Boys who have failed initial closure and/or are more than 6 mo old may be candidates for a combination of epispadias repair with bladder closure. Children should be carefully selected for combined or “complete” repair based on phallic size, length and depth of urethral groove, size of the bladder template, and perivesical and urethral plate scarring.

CONCLUSIONS

A modern staged approach to patients with bladder exstrophy provides a satisfactory outcome, both cosmetically and functionally in most cases. This approach consists of initial bladder and posterior urethral closure, early repair of epispadias, and bladder neck reconstruction. It is the recommended management based on the authors' and institutional experience treating more than 700 exstrophy–epispadias patients. Recent reports of a single-stage repair by other authors have purported

successful outcomes; however, follow-up is limited and the number of patients in these series is small. In a recent review of more than 80 patients, Chan et al. reported an 89% social continence rate within a group of selected patients treated using the aforementioned strategy (23). Although recent developments in tissue engineering hold promise to improve outcomes for patients requiring genitourinary reconstruction in the future, modern stage functional closure remains the “gold standard” for patients with classic bladder exstrophy.

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7

The Undescended Testis and Other Forms of Cryptorchidism

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TESTICULAR PROSTHESIS
POTENTIAL PITFALLS
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INTRODUCTION

The undescended testis (UDT) and other forms of cryptorchidism represent a group of genital anomalies commonly treated by the urologist. Although these conditions might seem to be simple abnormalities of the testes, cryptorchidism has a number of subtle and complex issues that must be considered separately in each clinical scenario. Some forms of cryptorchidism require no intervention, others are amenable to medical therapy, and others represent absolute indications for surgery. Therefore, a thorough understanding of the proper diagnosis of each of these conditions is required to provide proper management. The forms of cryptorchidism and relevant clinical issues are the subjects of this chapter.

ETYMOLOGY

The term cryptorchidism is derived from the Greek words “kryptos” and “orchis,” meaning hidden and testis, respectively, and refers to absence of a testis from the scrotum. Although the adjectives cryptorchid and undescended are often used interchangeably when referring to a testis outside the scrotum, they are not synonymous because cryptorchid testes may also be retractile, ascended, ectopic, or absent.

EMBRYOLOGY: TESTICULAR DEVELOPMENT AND DESCENT

Proper evaluation and management of cryptorchidism requires a thorough understanding of normal testicular development and descent. Development of a testis is determined at the time of conception by the presence of the SRY (sex-determining region Y-linked) gene on the short arm of the Y chromosome. During the fifth week of gestation, the testis begins to develop along the gonadal ridge in the retroperitoneum. Epithelial primary sex cords then grow into the underlying mesenchyma, resulting in the development of a cortex and medulla;

the cortex regresses and the medulla develops. Germ cells migrate from the yolk sac to the gonadal ridge during the fourth to sixth week of gestation, guided by chemotaxis. By the seventh week of gestation, the indifferent gonad begins to differentiate into a testis. At the eighth week of gestation, Sertoli cells appear and produce Müllerian inhibitory substance (MIS) to cause regression of the Müllerian ducts. Two weeks later, by the 10th week, Leydig cells appear and produce testosterone that results in development of the internal male genital duct structures by the 13th week of gestation. Development of the male external genitalia, including the scrotum, occurs between weeks 10 and 15 of gestation and results from the conversion of testosterone to dihydrotestosterone by the enzyme 5 α -reductase type 2 in the primordia of these tissues. This process is important because development of the scrotum allows for the ultimate descent of the testis from the abdomen.

After development, the testes descend in three separate stages. The first stage, transabdominal migration of the testis along the posterior body wall down to the internal inguinal ring, occurs during the latter part of the first trimester. This is a consequence of differential body growth and traction by the gubernaculum. The second stage of descent, development of the processus vaginalis and the inguinal canal, also occurs during the latter part of the first trimester, in the third month of gestation. The testis remains stationary at the internal inguinal ring during the second trimester. The third and final stage of descent, transinguinal migration of the testis to the scrotum, occurs at the beginning of the third trimester, between 24 and 28 wk of gestation (1).

TELEOLOGY

Descent of the testes into the scrotum is necessary for normal spermatogenesis at the time of maturity. Most authorities believe that the cooler environment of the scrotum, which is one to two degrees cooler than the abdominal cavity, is a key factor in normal spermatogenesis. Interestingly, the myth that wearing boxer shorts rather than briefs is favorable for men with infertility because of its temperature advantage has been proven false. The temperature of the scrotum is the same for men who wear either form of underwear (2).

TERMINOLOGY: THE FIVE FORMS OF CRYPTORCHIDISM

In addition to the UDT, cryptorchidism has four other forms: retractile testis, ectopic testis, absent testis, and ascended testis. Each of these conditions will be defined separately.

Undescended Testis

The UDT is a testis that has formed in the retroperitoneum and has come to rest somewhere along the normal path of testicular descent, without reaching the scrotum. The testis may be present in the abdomen, in the inguinal canal, or between the external inguinal ring and the scrotum in a prepubic position. A shortened spermatic cord, an indirect inguinal hernia, and epididymal abnormalities are common associated features.

Retractile Testis

The retractile testis represents the most common form of cryptorchidism and is a normal testis. It has completed the process of descent but tends to pull up out of the scrotum because of the cremasteric reflex, which is particularly strong and universally present in boys between the ages of 2 and 7 yr (3). This reflex is a consequence of the interaction of the spinal cord, the genitofemoral nerve, and the cremaster muscle. A retractile testis differs from a UDT because it can be manipulated into the scrotum, remains in the scrotum (at least temporarily) after its release, and is normal in size. Retractable testes should be monitored during childhood because they can, on some occasions, become truly undescended.

Ectopic Testis

An ectopic testis is one that has migrated outside the path of normal descent. The most common site of ectopia is the superficial inguinal pouch of Denis Browne, the space between Scarpa's fascia and the external oblique fascia above the external inguinal ring. Less common sites of ectopia include femoral, pubic, penopubic, penile, and perineal positions. In rare cases, a testis will cross into the opposite groin or scrotum, a condition known as transverse testicular ectopia. Ectopic descent is thought to result from abnormal development of the gubernaculum or from scrotal inlet obstruction. The accurate diagnosis of an ectopic testis, in contrast to an undescended or retractile testis, is important because the ectopic testis is fixed in position by fibrous attachments. Because it will not descend either spontaneously or with medical therapy, surgery is necessary to place it in the scrotum.

The Absent Testis

A unilateral absent testis, or monorchidism, occurs in 4% of patients with cryptorchidism; bilateral testicular absence, or anorchidism, occurs in less than 1%. Congenital absence of the testis may be caused by atrophy following testicular torsion *in utero* (resulting in a vanished testis) or testicular agenesis, which is a much more rare condition.

VANISHING TESTIS

The term vanishing testis was coined by Abeyaratne et al. (4) to describe the condition in which testicular vessels and a vas deferens, but not a testis, are found at surgical exploration. The cause of a vanishing testis is presumed to be torsion of the gonadal vessels *in utero* after development of the external genitalia (5). Supporting evidence includes hemosiderin and calcium deposits in testicular remnants found on exploration (6). Most cases of prenatal testicular torsion are thought to occur during descent of the testis through the inguinal canal in the third trimester. The presence of Wolffian duct structures and the absence of Müllerian structures indicates that an ipsilateral testis was present during gestation.

TESTICULAR AGENESIS

A testis may be unable to form in a 46, XY individual because the gonadal ridge fails to form or its blood supply fails to develop. Individuals with testicular agenesis may have either a male or a female phenotype. The variable phenotypic appearances, including the presence and form of the internal genitalia, relate to the time during gestation when the testis was lost. These findings are consistent with the classic experiments of Jost (7). The key clinical sign indicating testicular agenesis rather than a vanished testis is the presence of ipsilateral Müllerian structures. This entity is much less common than the vanishing testis syndrome. True congenital absence of one testis is extremely rare, and absence of both results in a female phenotype, regardless of the genotype.

Ascended Testis

An ascended testis refers to a cryptorchid testis, usually palpable, which had been previously and accurately identified as descended in the scrotum. In the past, this diagnosis was controversial and was considered to be a misdiagnosis resulting from an incomplete or inaccurate physical examination. However, the collective experience of good urologists over time suggests that this is a real phenomenon. Because reported cases are rare, a specific incidence has not been determined, but approx 2% of retractile testes are thought to become ascended.

Affected individuals usually are young boys of grade-school age. The cause is thought to be relative shortening or lack of elongation of spermatic cord structures as the child grows (8). This theory is supported by the usual finding of a fibrous remnant within the spermatic cord, which represents the obliterated processus vaginalis. This structure may limit growth of the spermatic cord and cause the attached testis to appear to ascend. Ascent of the testis may also be iatrogenic and may occur after an inguinal hernia repair when the testis is not properly

relocated in the scrotum. It is also common in those with cerebral palsy, with spasticity and relative shortening of the cremaster muscles over time leading to an ascended testis. Recognition of this entity is important, especially for primary care physicians, because the presence of a scrotal testis in early childhood does not exclude later testicular ascent. Therefore, scrotal examination during routine annual childhood check-ups is warranted.

FACTORS IN TESTICULAR DESCENT AND CAUSES OF CRYPTORCHIDISM

The observation by John Hunter in 1762 that the testis may fail to descend because it is intrinsically abnormal, rather than being abnormal because it fails to descend, remains a focus of investigation and debate. It is probably more correct to consider that both situations may exist at different times in different individuals. Some boys with cryptorchidism may have an intrinsically normal testis that, because of extrinsic factor(s) that prevent its descent, deteriorates over time. In other cases, a poorly developed testis may fail to descend because of intrinsic mechanical and hormonal factors that are abnormal.

The exact cause of cryptorchidism in any one particular case is often difficult to determine. On occasion, a specific anatomic or hormonal abnormality may be identified to suggest a cause. However, experiments in the laboratory and observations in nature have suggested the main factors related to normal testicular descent. These often go awry in cases of cryptorchidism.

Hormonal Factors

Hormones considered to play a role in testicular descent include androgens, MIS, epidermal growth factor, descendin, and estrogens (1). In rodents, Ins13 appears to play a role (9,10) but this finding has not been confirmed in humans (11). Of these hormones, androgens appear to be the most important. Evidence to support this includes the clinical syndromes with hypogonadism that are associated with bilateral cryptorchidism. However, the theory that androgens are exclusive in promoting testicular descent has been weakened by the finding that anti-androgens prevent testicular descent in only 50% of experimental animals, suggesting that other factors are also involved (12).

Mechanical Factors

Mechanical factors also play a critical role in the descent of the testis. These include the gubernaculum, the inguinal canal, the abdominal wall,

intra-abdominal pressure, the epididymis, and the genitofemoral nerve (1). Of these, the role of the gubernaculum appears to be most important. The elegant experiments of Frey and Rajfer suggest that the gubernaculum is important for testicular descent, that it need not be intact to serve this function, and that it probably serves to dilate the inguinal canal and form a path for the testis to follow (13).

CLASSIFICATION OF CRYPTORCHIDISM

For treatment purposes, cryptorchid testes are classified into palpable and nonpalpable varieties. Palpable cryptorchidism (80%) includes retractile testes; ascended testes; low UDTs; and ectopic testes that come to rest below the internal inguinal ring. Nonpalpable cryptorchidism (20%) includes the absent testis; UDTs that remain within the abdominal cavity; and small UDTs that cannot be felt within the groin or scrotum because of surrounding fatty tissue.

Palpable testes are usually treated with standard orchidopexy, except for the retractile testis, which is a normal testis and requires no intervention. Nonpalpable testes are treated surgically with initial exploration (either with diagnostic laparoscopy or by standard groin exploration) followed by further surgery dictated by the findings at exploration. In rare cases, radiographic imaging studies are performed before exploration; this will be discussed more fully later. Some may also choose to give human chorionic gonadotropin (hCG) injections to help make a nonpalpable testis become palpable or to facilitate orchidopexy if a testis is found (14).

INCIDENCE AND NATURAL HISTORY

Because testicular descent is completed during the third trimester of gestation, the incidence of cryptorchidism depends to some extent on the age of the child examined. Boys born prematurely have an incidence of cryptorchidism of approx 30%, which decreases to about 3% for full-term infants. By 1 yr of age, the incidence is approx 0.8%, representing 1 in 125 boys (15,16). Therefore, about two-thirds of cryptorchid testes will reach the scrotum by the time the boy is 1 yr old. Most UDTs that spontaneously descend will do so during the first 3 months after birth, and few will descend after that. Unilateral cryptorchidism (68%) is more than twice as common as bilateral cryptorchidism (32%), and the right side (70%) is affected more often than the left (30%) (17,18). Reports of the incidence of cryptorchidism may overestimate the true incidence if retractile or ascended testes are included in the data.

BILATERAL UDTs

Between 10 and 25% of patients with cryptorchidism have bilateral UDTs, representing approx 1 in 600 male births, and this can be a normal physical finding in premature male neonates (19). It is estimated that at least 6% of patients with bilateral UDTs have an endocrine disorder (20), such as hypogonadotropic hypogonadism, as the cause.

Bilateral Nonpalpable Testes

This condition represents a very special situation that may have life-threatening implications, especially in association with genital ambiguity. The differential diagnosis includes bilateral cryptorchidism, anorchidism, and ambiguous genitalia because of female pseudohermaphroditism or another intersex condition. The adrenogenital syndrome caused by congenital adrenal hyperplasia must be excluded. A karyotype, endocrine testing, and radiographic imaging studies provide the necessary information to make the diagnosis (Table 1).

When a male genotype is identified, endocrine studies may be useful to differentiate bilateral cryptorchidism from anorchia. The administration of hCG can stimulate testosterone production by testicular tissue so that its presence can be detected biochemically, and may also cause the gonads to become palpable by physical examination. However, false-negative hCG stimulation testing can occur because of an unresponsive population of Leydig cells (21). Therefore, hCG stimulation testing is combined with the measurement of gonadotropins to diagnose anorchia. Markedly elevated gonadotropin levels before puberty are indicative of anorchidism, (22) but all boys with normal serum gonadotropin levels must undergo exploration regardless of the outcome of the hCG stimulation test. Measurement of serum MIS can provide additional evidence that testicular tissue is present (23). Recent research also suggests that serum levels of inhibin B, a glycoprotein produced by Sertoli cells, is a good hormonal marker of testicular function and has the potential to become a diagnostic test for boys with cryptorchidism (24).

With a male genotype, and findings of a low serum testosterone level, a negative hCG stimulation test, increased serum gonadotropin levels, a negative serum MIS, normal levels of adrenal steroid precursors, and radiographic studies demonstrating the absence of Müllerian structures, the diagnosis of anorchia may be established. In equivocal cases, laparoscopy or open surgical exploration may be required to confirm the diagnosis (Table 1).

Table 1
Evaluation of Bilateral Nonpalpable Cryptorchidism

	<i>Cryptorchidism</i>	<i>Anorchidism</i>	<i>Female Pseudo-hermaphroditism</i>
Karyotype	46 XY	46 XY	46 XX
Serum Testosterone			
Baseline	normal	low	variable
HCG Stimulation Test	positive	negative	negative
Gonadotropins	normal	increased	normal
MIS	positive	negative	negative
Adrenal Steroid Precursors	normal	normal	increased
Ultrasound			
Gonads	testes or negative	negative	ovaries or negative
Internal Ducts	negative	negative	uterus/Müllerian system
Genitogram	male urethra	male urethra	urogenital sinus and/or Müllerian structures
Laparoscopy			
Gonads	testes	blind ending vessels	ovaries
Internal Ducts	Wolffian	Wolffian	Müllerian

Prune-Belly Syndrome

Prune-belly syndrome is the only condition of bilateral nonpalpable testes in a phenotypic male that does not require investigation as outlined above. In this case, the testes are usually found within the abdomen with an abnormally short and ectopic gubernaculum (25). The diagnosis of prune-belly syndrome is usually apparent by the wrinkled appearance of the abdominal wall.

RISK FACTORS

Risk factors for cryptorchidism include prenatal and postnatal environmental exposures and genetic factors.

Prenatal risk factors (in addition to prematurity) include maternal exposure to estrogens, such as diethylstilbestrol (26–28). Postnatal environmental risk factors, such as variation in seasonal daylight, have received some attention, but the available data are contradictory. New

attention is being focused on environmental estrogens as a potential risk factor for all forms of abnormal male genital embryology, including cryptorchidism (29).

Genetics probably represents the most significant risk factor for cryptorchidism. Although no specific, unique gene for UDT has been identified, cryptorchidism is known to cluster within certain families (30–33). Approximately 14% of boys with cryptorchidism come from families in which other males are also affected (16). Evidence suggests that cryptorchidism within a family is transmitted in a multifactorial pattern, with approx 4% of fathers affected and 6–10% of siblings affected (34,35). Although autosomal-dominant inheritance with incomplete penetrance has been suggested, studies of Mendelian chromosomal transmission in cryptorchidism have not proven this concept (36,37). Race does not seem to be a risk factor for this condition.

ASSOCIATED ANOMALIES

Because of the multiple factors involved in normal testicular descent, a wide variety of clinical syndromes that affect genetic integrity, and the endocrine, musculoskeletal, and nervous systems can be associated with this condition. Table 2 provides a few examples within each major category.

Within the genitourinary tract, the most common abnormality associated with UDT is a Wolffian duct abnormality, which occurs with an incidence of 30–79% (38–42). Abnormalities include various forms of epididymal detachment or malformation, such as an elongated epididymis. This is important because such abnormalities may contribute to infertility later in life, despite a technically successful orchidopexy.

Abnormalities of the urinary tract are not typically associated with UDT, and radiographic screening is unnecessary. However, in congenital absence of the vas deferens, a renal ultrasound should be performed to exclude renal agenesis.

UDT AND HYPOSPADIAS

The presence of UDT and hypospadias in the same individual requires special attention. In this situation, there is a significant incidence of intersex, which must be investigated and excluded (43,44). Mixed gonadal dysgenesis, with a mosaic karyotype and a streak gonad, is a common finding.

Table 2
Conditions Commonly Associated
with Cryptorchidism

Chrosomal disorders
XXY, XYY, XO/XY, XX male
autosomes 13, 18, 21
Hormonal disorders
Kallmann's Syndrome
Growth hormone deficiency
Neurologic disorders
Cerebral palsy
Spina bifida
Abdominal wall defects
Prune-belly syndrome
Gastroschisis
Omphalocele
Exstrophy
Syndromes
Prader-Willi
Laurence-Moon-Biedl
Noonan's
Beckwith-Wiedemann

DIAGNOSIS

History

Evaluation of the boy with cryptorchidism includes a thorough history from his mother regarding the use of drugs during pregnancy, such as sex steroids, that might impair testicular descent or cause ambiguous genitalia. Age of the child and any history of prematurity are noted. Family history of cryptorchidism, genetic or hormonal disorders, and anosmia is sought. Caretakers are asked whether the testis has ever been seen in the scrotum. A history of an inguinal mass or low abdominal pain may suggest an associated hernia or testicular torsion. If the child has had previous groin surgery, testicular ascent or secondary cryptorchidism must be considered. Individuals who are seen as adults and are sexually active may be questioned regarding evidence of fertility, including documentation of paternity and semen quality.

Physical Examination

Physical examination should be performed in a warm, comfortable room to minimize patient anxiety. A gentle manner and voice and playful distractions are helpful. Little boys can be very ticklish, with a strong cremaster reflex, and the examination may be difficult. A complete examination is performed for signs of clinical syndromes associated with cryptorchidism and for signs of virilization in older children and adults. Examination of the abdomen and flank is performed to identify any masses, scars, or hernias. The penis is examined to exclude micropenis and hypospadias, and the scrotum is examined for abnormal pigmentation and hypoplasia.

If one normal testis is present and descended in the scrotum, its size, shape, volume, consistency, and position are determined. Compensatory hypertrophy of a solitary scrotal testis may suggest absence of its mate (45) but this finding is variable and unreliable for a definitive diagnosis of monorchidism. The groin and spermatic cord on each side are palpated for evidence of an inguinal hernia and a vas deferens.

Physical search for a cryptorchid testis is best performed with warm hands to prevent a cremaster reflex and further difficulty in locating the testis. Lubrication of the hands with warm water and soap works well for this purpose. The warm soapsuds on the fingertips allow the fingertips to slide easily over the skin and improve the ability to feel a testis. Examining fingers are swept from the hip above the internal inguinal ring and along the inguinal canal toward the scrotum. All sites known for ectopic testicular migration are carefully examined. In contrast to lymph nodes, which are generally small, firm, and relatively fixed, palpable inguinal and ectopic testes are usually larger, softer, and somewhat mobile.

The child may be examined in several positions, including supine, sitting, squatting, and standing if the testis is difficult to identify. This is especially helpful for the older or obese child. One helpful maneuver is to have the child sit on the edge of the examining table with the physician seated on a chair in front of him. The child places his feet on the physician's thighs, and this creates a squatting position for the child above the level of the floor. The abdominal wall and scrotum become relaxed and a retractile or palpable UDT is then usually easy to feel.

If a testis is found, the location and physical characteristics are noted and compared with the descended mate. If the testis is retractile, it should easily reach the scrotum and remain there, at least temporarily, upon release. Difficulty differentiating the retractile from the low UDT may explain the varying success of hormonal therapy as well as why the

incidence of orchidopexy in some studies exceeds the expected incidence of cryptorchidism.

Some findings on physical examination are particularly helpful. Hypoplasia of the ipsilateral hemiscrotum suggests cryptorchidism with a testis that has never reached the scrotum on that side (Fig. 1). As mentioned above, compensatory hypertrophy of one testis suggests absence of the opposite mate.

INDICATIONS FOR TREATMENT

There are six main indications for treating the UDT (Table 3).

Fertility

Impaired fertility for those with untreated cryptorchidism is well documented, and those who have bilateral untreated UDTs eventually become sterile. This is because of pathologic changes that affect UDTs, including loss and atrophy of the seminiferous tubules, peritubular hyalinization, Leydig cell hyperplasia, and gradual loss of spermatogenesis, which may be detected microscopically starting at age 2 yr (46). Such microscopic testicular changes are manifest macroscopically as testicular atrophy, a late sign of testicular deterioration resulting from an abnormal extrascrotal position. Antisperm antibodies, abnormalities of the epididymis and vas deferens, and surgical injury to the vas deferens during orchidopexy may contribute to infertility in patients with cryptorchidism.

Cancer

Patients with a history cryptorchidism are at risk for developing carcinoma *in situ* of the testis, which is thought to be the precursor of invasive germ cell tumors in a high percentage of cases. This risk is significant for abdominal testes (25%), is much less for inguinal testes (0.68%), and is approx 0.5 to 1.5% for boys treated by early successful orchidopexy (47). Consequently, the risk of developing a testicular tumor for those born with a UDT is increased about 40-fold over the general population (risk 1/100,000) to approx 1 in 2500. Testes treated by orchidopexy most commonly develop seminoma, whereas untreated UDTs most commonly develop embryonal carcinoma (48). The incidence of malignant degeneration increases with the higher location of the UDT; intra-abdominal testes comprise 14% of UDTs but develop nearly 50% of associated testicular tumors (49). To date, there is no clear evidence that orchidopexy surgery prevents future development of tes-



Fig. 1. Hypoplasia of the hemiscrotum indicates that the testicle has never descended.

Table 3
Indications for Treatment
of Cryptorchidism

Fertility
Malignancy
Inguinal hernia
Torsion
Trauma
Mental health

ticular tumors. However, proper placement of a testis in the scrotum allows early detection and treatment of this entity, if necessary. It is also important to remember that a testicular tumor may develop in a contralateral normal descended testis; this occurs in about 20% of orchi-dopexy patients in whom a testicular tumor ultimately develops (48,50).

Inguinal Hernia

Because closure of the processus vaginalis is the last step in testicular descent, indirect inguinal hernia is commonly associated with UDT and may not be detected preoperatively by history or physical examination.

The higher the testis at the time of surgery, the more likely it is that an inguinal hernia will be found.

Testicular Torsion

Testes that are not properly fixed in the scrotum are at risk for testicular torsion. This possibility should be considered for the child with an empty hemiscrotum who has abdominal or groin pain and no prior surgery. Torsion of an intra-abdominal testis may cause an acute abdomen and may also reflect the presence of an intra-abdominal testicular tumor, which is found in up to 60% of such cases (51,52).

Trauma

Testes in the scrotum are mobile and are protected from blunt trauma by the cremaster reflex, and testes in the abdominal cavity are protected by the abdominal wall. Testes resting against the pubis, however, are subject to crush injury from blunt trauma as might occur during contact sports.

Mental Health

Although there is not much formal data regarding the effect of an empty hemiscrotum on a boy's mental health, the effect of this condition on his body image and self-esteem are probably real and significant additional factors to consider in a review of the indications for treatment.

RADIOGRAPHIC IMAGING AND LOCALIZATION STUDIES

Historically, radiographic localization studies have been used to identify the nonpalpable testis. The rationale for these studies has been that those with absent testes could be spared unnecessary surgery, and those with inguinal or abdominal testes could receive a properly tailored operation. Studies such as pneumoperitoneography, contrast herniography, arteriography, and spermatic venography have been used. However, these localization techniques have fallen into disfavor for the following reasons:

1. The techniques are expensive.
2. The techniques are invasive.
3. The techniques are relatively difficult to perform.
4. The patient must be exposed to radiation.
5. The patient must be given a general anesthetic.
6. The studies, most importantly, are unreliable.

Modern imaging techniques such as ultrasound, computed tomography, and magnetic resonance imaging are noninvasive, easier to perform, and more accurate in identifying an intra-abdominal testis, but even these studies can be associated with a false-negative rate of up to 20% (Table 4).

Localization studies are helpful only when they can guide clinical management. Unfortunately, all radiographic localization studies suffer from deficiencies in sensitivity and specificity (Table 4), and none can prove that a testis is absent. Furthermore, radiographic imaging for a cryptorchid testis is only 44% accurate overall (53). For these reasons, and because of the potentially serious consequences of a false-negative study, radiologic imaging is generally not recommended for routine localization of a unilateral nonpalpable testis. Because such imaging must be followed by surgical exploration, regardless of the results, it is also usually unnecessary.

At this time, diagnostic laparoscopy is the easiest, most accurate, and therefore the best way to look for a nonpalpable testis. Nevertheless, radiographic imaging studies may be useful preoperative adjuncts in certain clinical circumstances. Scrotal-inguinal ultrasound may help identify nonpalpable inguinal testes in overweight or uncooperative boys and may help provide regular follow-up of adolescents who, because of comorbid conditions, are not surgical candidates (54). It may also be helpful for those who have relative or absolute contraindications for diagnostic laparoscopy.

HORMONAL THERAPY

Hormonal therapy for cryptorchidism is based on the evidence that failure of a testis to descend is associated with hypogonadism. Various agents have been used for this purpose, including hCG, which is structurally similar to luteinizing hormone (LH), luteinizing hormone-releasing hormone (LH-RH), and Buserelin (a synthetic superanalog of LH-RH). All of these agents have a similar mechanism of action, i.e., to cause testosterone production by the testes to stimulate testicular descent. Direct systemic testosterone therapy is ineffective for this purpose because a high *local* level of testosterone is important to stimulate testicular descent.

hCG is the only hormonal agent approved by the Food and Drug Administration for the treatment of cryptorchidism in the United States today. It is used for retractile testes and is approx 85% effective. It is also used for UDTs and is 15% effective, with a slightly better efficacy for bilateral UDTs, but still with a success rate of less than 25%. A typical dosage schedule is 15,000 units intramuscularly given over 1 mo (e.g.,

Table 4
Accuracy of Radiographic Localization Studies

	<i>TP/TP+FN</i> <i>Sensitivity</i>	<i>TN/TN+FP</i> <i>Specificity</i>	<i>FP</i>	<i>FN</i>
Ultrasound (<i>n</i> = 23) (<i>53a</i>)	88%	100%	0	2
Ultrasound (<i>n</i> = 22) (<i>53b</i>)	62%	76%	1	4
CT (<i>n</i> = 23) (<i>53c</i>)	94%	100%	0	1
CT (<i>n</i> = 23) (<i>53d</i>)	100%	83%	4	0
MRI (<i>n</i> = 22) (<i>53b</i>)	100%	69%	5	0

TP, true positive; TN, true negative; FP, false positive; FN, false negative; CT, computed tomography; MRI, magnetic resonance imaging.

2500 units given twice a week for 3 wk before surgery). Temporary side effects may include penile growth, erections, weight gain, and hyperactivity. No apparent central nervous system effects have been reported to date. The dosing is limited to a total of 15,000 units to prevent premature closure of the epiphyseal plate and limited growth of the long skeletal bones. The contraindications to hCG therapy are listed in Table 5 (1).

SURGICAL THERAPY

The six options for surgical therapy of cryptorchidism are listed in Table 6. Each of these will be covered below after a brief discussion of the relevant surgical anatomy.

Surgical Anatomy

The testis is supplied by the structures of the spermatic cord within the inguinal canal. The spermatic cord contains the ilioinguinal (L1) and genital branch of the genitofemoral (L1-L2) nerves, the cremaster muscle, the testicular vessels, the vas deferens, sympathetic and parasympathetic nerves, and the remnants of the processus vaginalis. The fascial coverings of the spermatic cord are the extensions of the abdominal counterparts: the external spermatic (external oblique), cremasteric or middle spermatic (internal oblique), and internal spermatic (transversalis) fascia.

The primary arterial blood supply of the testis is the testicular artery, also termed the gonadal or internal spermatic artery, which is a branch of the abdominal aorta. Additional collateral blood supply comes from the cremasteric, or external spermatic, artery and the artery of the vas deferens, branches of the inferior epigastric and inferior vesical arteries, respectively. Minor collateral contributions come from the anterior and posterior scrotal arteries, which are branches of the pudendal artery (55). Venous drainage of the testis is through the pampiniform plexus

Table 5
Contraindications for Hormonal Therapy of Cryptorchidism

<i>Contraindication</i>	<i>Rationale</i>
Neonatal period and early infancy	The testis may still descend spontaneously
Prior inguinal surgery	Inguinal scarring will prevent testicular descent
Ectopic testis	An abnormal gubernaculum insertion will prevent testicular descent to the scrotum
Clinical inguinal hernia	The hernia will not close with hormonal therapy
Prune-belly syndrome	Syndrome includes high abdominal testes with abnormal gubernacula, which will not descend with hormone therapy
Postpuberty	The testes are already producing endogenous testosterone, so additional stimulation is unnecessary

Table 6
Options for Surgical Therapy of Cryptorchidism

- | |
|--|
| <ol style="list-style-type: none">1. Standard orchidopexy2. Fowler-Stephens orchidopexy3. Microvascular autotransplantation4. Laparoscopic orchidopexy5. Staged orchidopexy6. Orchiectomy |
|--|

of veins, which drains through the gonadal vein into the renal vein on the left and the inferior vena cava on the right. The gonadal vessels course in the retroperitoneum ventral to the ureter before entering the internal inguinal ring just lateral to the inferior epigastric vessels. Venous drainage of collateral vessels follows their arterial counterparts. It is important to recognize the indirect course of the testicular vessels to take advantage of additional vascular length available during orchidopexy (56). Lymphatic drainage is to the retroperitoneal lymph nodes, but may be altered after orchidopexy to include the superficial inguinal lymph nodes. Therefore, it is also important to keep in mind that if a testicular tumor develops after orchidopexy, the inguinal lymph nodes may be the first affected by metastatic disease (57).

Standard Inguinal Orchidopexy

The technique of standard inguinal orchidopexy has undergone some refinement over time as our understanding of surgical anatomy and the development of surgical techniques have improved. The principles of standard orchidopexy, as originally described by Bevan in 1899 (58) include isolation and mobilization of the testis, with preservation of the structures of the spermatic cord, high ligation of the inguinal hernia sac, and fixation of the testicle in the scrotum. The technique described here covers the standard technique for the palpable cryptorchid testicle, which represents the majority of undescended and ectopic testes.

The approach in the operating room should begin with a repeat physical examination before or after induction of anesthesia, and at both times if possible. Any new findings regarding the position and/or palpable nature of the cryptorchid testis is then used in the preoperative planning and surgical technique.

A transverse skin incision within Langer's lines is made over the inguinal canal from a point above the internal inguinal ring (the midway point between the pubic tubercle and the anterior superior iliac spine) extending medially to a line drawn vertically along the lateral aspect of the ipsilateral hemiscrotum (Fig. 2). The incision is typically about 1 inch in length but is adjusted for clinical circumstances. The subcutaneous tissue is divided sharply, the superficial inferior epigastric vessels are cauterized or ligated, and the inguinal canal is opened sharply while preserving the ilioinguinal nerve. Handheld or self-retaining retractors are placed for exposure, and cremasteric muscle fibers are bluntly separated using the tips of a curved hemostat.

The testis is delivered, and dissection is then immediately directed distally, toward the gubernaculum, with special care to avoid injury to a long-loop vas deferens or an elongated epididymis (Fig. 3). The gubernaculum is divided, and any tethering slips of cremaster muscle are teased away or carefully divided to allow extension of the spermatic cord. It is helpful to remember that dividing the cremaster muscle insertion will eliminate the usefulness of the cremaster reflex for any future evaluation of an ipsilateral acute scrotum. The internal spermatic fascia (an extension of the transversalis fascia) is then opened along the posterior aspect of the spermatic cord, where it stops near the internal inguinal ring. Passing the tip of a small hemostat beneath the internal spermatic fascia at this point is helpful to protect the spermatic cord structures. This maneuver allows direct access to the processus vaginalis.

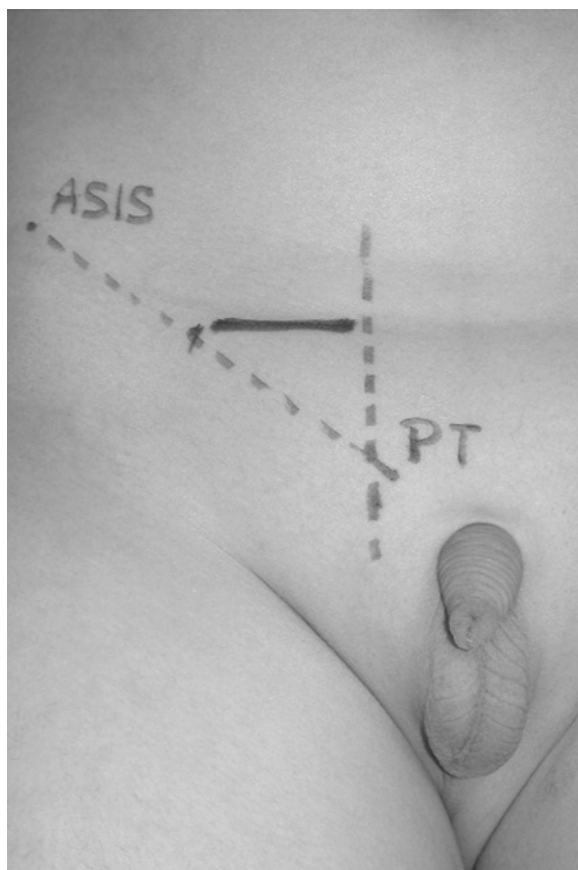


Fig. 2. A proper skin incision for a standard inguinal pediatric orchidopexy. The incision extends from a point corresponding with the position of the internal inguinal ring (midway between the ASIS and the pubic tubercle), medially and transversely within Langer's lines, to a line vertically through the lateral margin of the scrotum. ASIS, anterior superior iliac spine; PT, pubic tubercle.

If a testis is not found in the inguinal canal but was palpable preoperatively, the next step is to open the peritoneum to look for the testis within the abdominal cavity, because a search for the testis in the retroperitoneal space will be unrevealing. It is not uncommon for a palpable UDT to fall back into a hernia sac and become nonpalpable within the abdomen at the time of surgery.

Separation of the processus vaginalis, or indirect inguinal hernia sac, from the adjacent spermatic cord structures is then performed. This is the most important maneuver during orchidopexy, because it provides most



Fig. 3. An elongated epididymis is commonly found attached to an undescended testis, especially with high inguinal or abdominal testes. It is important to carefully trace the epididymis and vas deferens distally to their most caudal points before dividing the gubernaculum to avoid injuring these structures. Note the extremely long epididymal tail (arrow) extending below the scrotum during this routine inguinal orchidopexy.

of the relaxation on the testicular vessels to allow the testis to reach the scrotum without tension. The hernia sac is dissected up to the level of the internal inguinal ring and ligated at that position with absorbable suture.

If additional length on the testicular vessels is necessary, the lateral tethering bands of Denis Browne may be divided. Dissection may continue proximally into the retroperitoneum to mobilize the peritoneum off the testicular vessels and provide their further extension distally toward the scrotum.

If further vascular length is desired, a Prentiss maneuver can be performed to pass the testicular vessels medial to the inferior epigastric vessels and provide a straighter course for them to the scrotum (56). The transversalis fascia over the inferior epigastric vessels is carefully divided to expose them. Rather than dividing these vessels, a better option is to pass the testis and testicular vessels behind the preserved inferior epigastric vessels, preventing the possibility of postoperative bleeding at that site.

Once adequate length on the testicular vessels is established, the tunica vaginalis is opened to expose the testis and epididymis. Any abnormality of these structures is identified and recorded. The appendix

testis, present in 92% of cases (59) is identified and removed to prevent an acute scrotum in the future as a result of torsion of the appendix testis.

A dartos (sometimes called a subdartos) pouch is then created in the ipsilateral hemiscrotum in standard fashion. Care is taken to avoid crossing the scrotal midline. A hemostat is passed from the scrotal incision up to the inguinal incision, and the testis is delivered to the scrotum by traction on the divided gubernaculum. The spermatic cord is inspected to exclude tension or torsion. To secure the testis, fixation sutures are placed between the dartos fascia and either the tunica vaginalis or tunica albuginea on each side of the testis. Care is taken to avoid the testicular vessels as they penetrate and course through the surface of the testis. The testis is placed in the subdartos pouch, local anesthetic is injected for postoperative comfort, and the incisions are closed anatomically in layers with absorbable sutures.

Testicular Biopsy

The role of testicular biopsy during routine orchidopexy is controversial. A small group of pediatric urologists advocate testis biopsy and are using the information for research regarding the potential usefulness of postoperative hormonal therapy with gonadotropin-releasing hormone agonists to improve later spermatogenesis. Although initial data from this group suggests that this approach may be helpful for future fertility (60) there are also contradictory data (61). Because this work is experimental, most urologists do not perform testis biopsy during orchidopexy, except in very unusual circumstances. Such circumstances might include orchidopexy in the older child, to exclude a diagnosis of Sertoli cell only (or carcinoma *in situ*) within the affected testis (62). Routine testis biopsy during orchidopexy is currently not recommended except during approved clinical trials because it may injure the involved testis or epididymis (which may be a solitary testis), and because, given the advanced state of assisted reproductive technology today, the biopsy results may cause unnecessary stress to the patient and family and provide little, if any, useful information for improving future fertility.

SURGERY FOR THE UNDESCENDED OR ECTOPIC TESTIS WITH SHORT TESTICULAR VESSELS

The limiting factor for successful orchidopexy is usually the length of the testicular vessels. If these vessels are short, then three other options for orchidopexy are considered: Fowler-Stephens orchidopexy (FSO), laparoscopic orchidopexy, and microvascular autotransplantation.

Fowler-Stephens Orchidopexy

This surgical approach was described by Fowler and Stephens in 1959 (63). The testicular vessels are divided, and the testis survives on its collateral blood supply through the cremaster and vas deferens arteries. It is very important to preserve the peritoneal tissue between the vas and testicular vessels during this procedure to help maximize the remaining blood supply.

An FSO may be done in one or two stages. For a one-stage procedure, the vessels are divided and the testis is transferred to the scrotum during the same procedure. In a two-stage procedure, the testicular vessels are divided, but the testis is left *in situ* to allow for development of better collateral blood supply over time. The second stage, placement of the testis in the scrotum, is done 3–6 mo later. If a two-stage FSO is performed, the first stage may be done easily after diagnostic laparoscopy, with laparoscopic clipping of the testicular vessels (64). In either case, division of the testicular vessels close to the testis is suggested to allow maximal cross-circulation from the testicular artery to the collateral vessels (65).

Laparoscopic Orchidopexy

This approach has developed over the last decade and has become quite popular with those experienced with laparoscopic surgery. The specific details of the technique have been previously described (66). The advantages of this approach are that it is a minimally invasive operation that provides improved visualization, there is a magnified surgical image, there is easy access to the upper retroperitoneum, and there is wide mobilization of the testicular vessels. The disadvantages include the cost of the laparoscopic instruments and the time and experience needed to master the technique. The complications of laparoscopic surgery are most significant for the inexperienced laparoscopic surgeon, but results are much improved after 100 procedures (67).

Microvascular Autotransplantation

It is important to remember that the kidney is not the only organ in urology that can undergo transplantation. In special situations, such as for a high solitary testis or bilateral high intra-abdominal testes, this may be the procedure of choice to help prevent testicular atrophy. Such testes can be transferred to the scrotum by dividing the testicular vessels within the abdomen and re-establishing the blood supply to the testis by means of a microvascular anastomosis with the inferior epigastric vessels near the scrotum. This procedure has a high success rate and a low rate of

testicular atrophy, as low as 4% (68). The disadvantages of this approach include the requirements of a long and arduous procedure, special technical expertise for the microvascular anastomosis, and careful postoperative management, which may include hospitalization and bedrest for several days and a urethral catheter to prevent bladder distension, to help ensure a successful result. For these reasons, testis autotransplantation is usually not performed when a normal scrotal testis is present on the opposite side of the high UDT, but this decision may be left to the individual surgeon and the patient and his family. It is probably most useful for patients with a high, solitary UDT, those who have a high UDT with a prior contralateral orchidopexy failure, and those patients for whom FSO not possible, such as those with congenital absence of the vas deferens.

OTHER SURGICAL OPTIONS FOR THE UDT

Staged Orchidopexy

Mentioned here for completeness and historical purposes, staged orchidopexy refers to an orchidopexy procedure that is interrupted because of an inability to place the testis in the scrotum because of short testicular vessels. The testicle is left in an undescended position, sometimes wrapped with a protective covering (such as Silastic), and a second stage of surgery is attempted later after the testicular vessels have had a chance to grow longer. It is likely that any orchidopexy success at a second stage of surgery is the result of better mobilization rather than growth of the testicular vessels (69). With today's advanced techniques, staged orchidopexy (except for two-stage FSO) is almost never performed and is never planned.

Orchiectomy

The final surgical option for a testis that is poor in quality or for which orchidopexy is technically impossible is orchiectomy. This may be performed laparoscopically or by standard open surgical techniques.

SURGICAL MANAGEMENT OF THE NONPALPABLE TESTIS

Management of the nonpalpable testis in the operating room begins with a repeat physical examination with the patient under anesthesia to exclude a palpable testis. If none is found, diagnostic laparoscopy is performed in standard fashion through the umbilicus. One of three possible findings will be encountered:

1. Testicular vessels will be found ending blindly within the abdomen, indicating a vanished testis. This occurs in 16% of cases. Note that an absent or blind ending vas deferens does not indicate absence of the testis.
2. Testicular vessels will be found entering the inguinal canal, indicating a testis or testicular remnant in the groin or the scrotum. This occurs in 45% of cases.
3. A testis will be found visible within the abdomen. This occurs in 38% of cases (1).

In the case of a vanished testis, further ipsilateral exploration is unnecessary, and laparoscopy is terminated. Fixation of the contralateral testis to prevent future torsion may be performed through a small contralateral scrotal incision based on the individual surgeon's preferences.

When testicular vessels are seen entering the inguinal canal, a groin exploration is performed to look for a testis. If a healthy-appearing testis is found, standard inguinal orchidopexy is performed. Sometimes, however, a small, atrophic, testicular remnant or nubbin is identified. Because this tissue may contain germ cell elements that may theoretically undergo malignant transformation, most authorities recommend its removal. Whether or not the nubbin is removed, contralateral testicular fixation may be performed just as for cases of monorchidism caused by a vanished testis.

If a testis is found within the abdomen, an orchidopexy is attempted in one of the manners described for dealing with UDT with short testicular vessels. Because a laparoscopic procedure has already been started, laparoscopic orchidopexy may be the easiest and most reasonable approach in this situation. Another option is the Jones approach for the nonpalpable testis, which uses a muscle-splitting extraperitoneal incision to gain access to the testis above the internal inguinal ring and may allow a similar surgical approach without the use of laparoscopic instruments (70).

INCIDENTAL FINDINGS

At the time of orchidopexy, ectopic tissue may be identified adjacent to the testis. Examples include spleen and liver tissue because of splenogonadal and hepatogonadal fusion and adrenal tissue in the form of an adrenal rest. Intra-abdominal structures may descend into a patent processus vaginalis and be present in a hernia sac in the spermatic cord. Examples include abdominal viscera, such as bowel and omentum, and pelvic viscera, such as the bladder. In rare cases of MIS deficiency,

Müllerian structures may be found as an interesting surprise within a hernia sac. Preoperative awareness and intra-operative recognition of these variations in anatomy should allow proper surgical management and prevent complications.

SPECIAL CIRCUMSTANCES

Special circumstances in dealing with the UDT deserve particular mention. The large or obese child may benefit from preoperative hCG stimulation to increase blood supply to the testis and make orchidopexy technically easier. Similarly, bilateral high UDTs may be best treated with preoperative hCG stimulation and staged individual inguinal orchidopexies (i.e., a right orchidopexy followed by a left orchidopexy at a separate time, as opposed to a staged orchidopexy on a single testis) to avoid the risk of bilateral testicular atrophy. If atrophy occurs after the first orchidopexy, an alternative surgical approach, such as microvascular autotransplantation, may be considered for the second orchidopexy.

After puberty, one should consider orchiectomy for a UDT that demonstrates atrophy, especially with a normal contralateral mate, because it is likely to show Sertoli cell only on pathologic examination (62). Intra-operative testicular biopsy may be helpful to support this approach.

It is also important to remember that following an FSO, vasectomy as an adult is contraindicated because it may interrupt the remaining collateral blood supply to the testis.

The finding of a UDT in the scrotum when the patient is under general anesthesia may present a dilemma. However, if a proper and thorough physical examination was done before surgery, it may be presumed that the testicle will ascend out of the scrotum after reversal of anesthesia because of recurrent shortening of the spermatic cord structures. Therefore, although one may abort the plans for surgery, proceeding with orchidopexy is also a reasonable option in these circumstances.

RE-OPERATIVE ORCHIDOPEXY

Orchidopexy may need to be performed after a prior groin operation or orchidopexy because of testicular ascent or retraction. The procedure is inherently more difficult because of the regional scarring. A helpful technique has been previously described to deal with this situation (71). Basic principles for this surgery include the following:

1. There must be early and initial isolation of the testis, even if that requires a scrotal incision, followed by slow and careful proximal dissection through both an inguinal and scrotal incision.

2. The spermatic cord must be widely mobilized, leaving a strip of external oblique fascia attached to the cord, if necessary, because of adherent scarring between these tissues.
3. The peritoneum must be mobilized high above the site of any prior surgery to free any residual attachments from a hernia/hydrocele sac to the spermatic cord.
4. The testis must be fixed securely within the scrotum.

POSTOPERATIVE FOLLOW-UP

Proper management of cryptorchidism does not end in the operating room. After orchidopexy, the child should be seen in 2 wk to assess wound healing and check testis position. A second postoperative visit is made 3 mo later to reconfirm testis position and exclude atrophy. Annual scrotal examinations are then recommended during routine visits with the primary care physician. Proper development of secondary sexual characteristics and testicular growth is assessed at puberty, especially for those with a history of bilateral cryptorchidism or delayed surgical correction. Finally, patients are seen after puberty at the age of maturity to teach the technique and the importance of testicular self-examination.

PATIENT AGE AND RECOMMENDED MANAGEMENT

For the full-term boy under the age of 6 mo, proper management includes observation with serial examination because testes may descend spontaneously during early infancy. Between the age of 6 mo and 2 yr, if a testis is not in the scrotum, definitive medical or surgical management should be carried out because after the age of 2 yr, histologic deterioration of a UDT (and even its contralateral descended mate) can be observed. Orchidopexy later in childhood is reasonable for healthy-appearing testes, but orchiectomy may be a better option for poor-quality testes or for a UDT after puberty. Historical reports have suggested that the benefit of removing a UDT to prevent future malignancy after the age of 32 is outweighed by the risks of anesthesia (72). However, given the advances of better anesthetic agents and techniques over the last two decades, it is now probably more reasonable to search for and remove UDTs in adults, which may be done by either open or laparoscopic surgical techniques.

TESTICULAR PROSTHESIS

A testicular prosthesis is available and is offered to those boys with congenital or surgical absence of a testis. Models commercially avail-

able in the United States today are composed of solid silicone or plastic because of the well-known health concerns of using silicone gel prosthetics. Placement of a testicular prosthetic may be performed in infants and small children, if requested, but deferring such surgery until the age of adolescence is preferable because it will preclude the need to replace an infant-sized prosthesis with an adult-sized one. For those who request a prosthesis, it is very important to implant it through an inguinal incision to prevent extrusion through a suture line on the scrotum (73).

POTENTIAL PITFALLS

Potential pitfalls in the management of cryptorchidism include, but are not limited to, the following:

1. Misdiagnosis of a UDT as a retractile testis, which may result in delayed proper management and histologic deterioration.
2. Failure to examine retractile testes annually, which may result in a missed future ascended testis.
3. Iatrogenic tension or torsion on the spermatic cord during orchidopexy, which may lead to orchidopexy failure resulting from testicular retraction or atrophy.
4. Injury to the spermatic cord structures or epididymis during orchidopexy, which may adversely affect testis and tubular function and can easily occur in cases in which there is a long-loop vas deferens or epididymis.
5. Inadequate preservation of collateral blood supply during a FSO, which may result in testicular atrophy.
6. Incomplete surgical exploration for a nonpalpable testis, which may leave a testis in the abdominal cavity or lead to the removal of an inaccurately identified vanished testis from the groin or scrotum. This pitfall may be avoided by thorough surgical exploration with or without diagnostic laparoscopy and clear identification of the termination of the testicular vessels.

COMPLICATIONS

Fortunately, in experienced hands, complications after surgery for cryptorchidism are uncommon. Complications include testicular retraction (3–5%), testicular atrophy (1–3%), injury to the vas deferens (< 1%), iatrogenic or incidental future testicular torsion (< 1%), and surgical infection (< 1%). In addition, although they are not a complication of surgery per se, testicular tumors will ultimately develop in 0.04% of patients with a UDT, and it is important to keep this in mind.

SURGICAL OUTCOMES

Current surgical therapy is quite effective at reaching its intended goals. Because it is difficult to assess orchidopexy success in children based on testicular function, success is generally considered to be a scrotal testis without atrophy. Standard inguinal orchidopexy in young boys is associated with a success rate of 92% (74). More modest success rates are seen in children over the age of 6 yr, those with high testes prior to surgery, and those who undergo FSO (division of the testicular vessels). A pair of recent reports also indicate that laparoscopic orchidopexy is better than either a one- or two-stage FSO, based on the previous definitions of success (Table 7) (75,76).

SUMMARY

Cryptorchidism represents a diverse but interrelated group of abnormalities of testicular position and includes the undescended, retractile, ectopic, absent, and ascended testis. The distinctions between each of these separate diagnoses may, at times, be difficult to determine but are important to provide proper management. A normal scrotal examination in early infancy does not eliminate the possibility of later testicular ascent, which may occur with some frequency in the retractile testis group. Therefore, routine annual scrotal examination from early childhood through puberty by primary care physicians is recommended to help detect and treat the ascended testis.

The case of bilateral nonpalpable testes in a phenotypic male deserves special attention because of the potentially serious consequences if a diagnosis of adrenogenital syndrome is overlooked. Similarly, in the case of concurrent cryptorchidism and hypospadias, the possibility of an intersex state should be considered and investigated.

Because histologic deterioration of a cryptorchid testis can occur as early as 2 yr of age, treatment before this time is best. Radiographic localization studies for the nonpalpable testis are generally unnecessary except in special situations, and diagnostic laparoscopy represents the easiest and most accurate way to look for a nonpalpable testis today. Hormonal therapy with hCG is one of the treatment options and is most useful to diagnose and treat the retractile testis. hCG therapy has modest efficacy for the low UDT but may provide significant benefit as a preoperative adjunct before an anticipated difficult orchidopexy.

Surgical therapy today is based on the general principles defined by Bevan more than 100 years ago. However, the contributions of the Fowler-Stephens team, as well as the use of microvascular autotransplantation techniques and advanced laparoscopic instruments, have

Table 7
Surgical Results for Laparoscopic Orchidopexy

<i>Technique</i>	<i>N</i>	<i>Rate of Atrophy</i>	<i>Not in Scrotum</i>
Laparoscopic orchidopexy	168	2.4%	1.2%
One-stage Fowler-Stephens	19	21%	0
Two-stage Fowler-Stephens	56	7.1%	1.8%

From ref. 75.

improved therapy. A surgical success rate of greater than 90%, based on the pediatric anatomic definition, is reasonable to expect for standard inguinal orchidopexy, although the rate may be slightly lower for more difficult orchidopexy cases involving short testicular vessels. All boys, especially those with a history of cryptorchidism, should ultimately be taught testicular self-examination, either by their primary care physician or by a urologist, to allow for early detection of a testicular malignancy as an adult.

Further research is needed to help identify the specific causes of testicular maldescent, less invasive ways of providing effective treatment, and other ways to help minimize the morbidity associated with this condition. Nevertheless, by following the general principles in this chapter for the evaluation and management of cryptorchidism, the practicing urologist can expect consistent and favorable clinical outcomes.

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8

Duplicated Ureters and Ureterocele

Christopher S. Cooper, MD

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INTRODUCTION

Ureteral duplications are a common anomaly, occurring in approx 1 in 125 people (1,2). Duplications are seen in patients of any age and in variable ways, including hydronephrosis detected on prenatal ultrasound, urinary tract infections (UTI), incontinence, and even urinary tract obstruction. Often a high index of suspicion must be maintained to diagnose ureteral duplication. The presence of multiple ureters requires a standard terminology to describe the patient's anatomy. The complexity of ureteral duplication anomalies is best understood using a basic background of normal ureteral embryology. Following a brief review of the terminology and embryology, this chapter will discuss ureteral duplication, ureterocele, and ectopic ureters.

TERMINOLOGY

A standard set of definitions was established by the urologic section of the American Academy of Pediatrics Committee on Terminology, Nomenclature, and Classification to describe ureteral duplication anomalies (3). A duplex (duplicated) system refers to a kidney with two pelvicalyceal systems. If this kidney has two ureters that empty sepa-

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rately into the bladder (double ureters), it is considered a complete duplication. A duplex system may also have a partial or incomplete duplication in which a single ureter enters the bladder. A bifid pelvis contains two pelvicalyceal systems joining at the ureteropelvic junction, and bifid ureters join before reaching the bladder.

The upper or lower pole ureter describes the ureter draining the upper or lower pole of a duplex kidney. The orifice associated with the ureter draining the upper or lower pole is known as the upper or lower pole orifice, respectively. A laterally ectopic ureter inserts lateral to the normal position, and a medially or caudally ectopic ureter inserts medially and distally to the normal position on the trigone. An ectopic ureter generally refers to an orifice located medially or caudally.

A ureterocele is a cystic dilation of the intravesical submucosal ureter. Ureteroceles contained entirely within the bladder are intravesical ureteroceles. Ectopic ureteroceles contain a portion permanently situated at or distal to the bladder neck. A single-system ureterocele is associated with a kidney containing only one ureter. A duplex-system ureterocele occurs with the upper pole ureter of a duplex kidney.

EMBRYOLOGY

The ureteral bud arises from the mesonephric (Wolffian) duct at the end of the fourth week of gestation and penetrates the metanephric blastemal ridge (Fig. 1). The ureteric bud then forms the ureter, renal pelvis, calyces, papillary ducts, and collecting tubules. The metanephros differentiates into the more proximal portions of the kidney.

The common excretory duct is that portion of the mesonephric duct between the origin of the ureteric bud and the cloaca. This segment expands and is incorporated into the urogenital sinus by the eighth week of development. With development, the ureteral orifice migrates cephalad and laterally, and the mesonephric duct moves distally and medially. By the 12th week of gestation, the mesonephric duct reaches its final entry position in the posterior urethra at the level of the verumontanum in the male. The mesonephric duct becomes part of the epididymis, seminal vesical, and vas deferens in the male and part of the Gartner's duct in the female.

Incomplete ureteral duplication results from a ureteral bud bifurcating after its origin from the mesonephric duct. A complete duplication with two ureters requires two ureteral buds arising from the mesonephric duct. A ureteral bud originating at a lower-than-normal position on the mesonephric duct undergoes early incorporation into the urogenital sinus and migrates more laterally and cranially than normal. In this

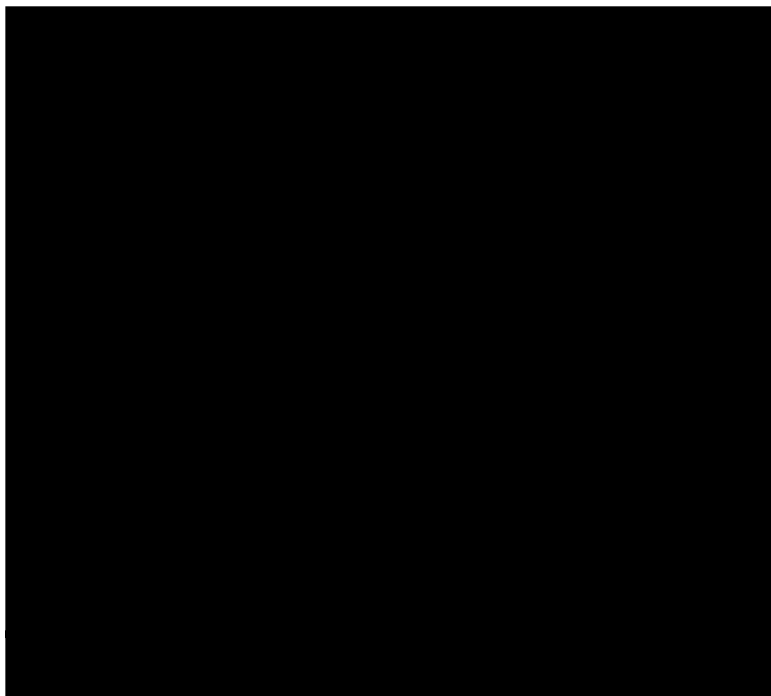


Fig. 1. Normal embryology of ureteral bud from the mesonephric duct penetrates the metanephric blastemal ridge. From ref. 3a. Reprinted with permission.

position, less trigonal support for the ureter might be expected, permitting vesicoureteral reflux (VUR) (4–6). The Meyer-Weigert law states that when complete ureteral duplication exists, the medial and distal ureteral orifice is from the ureter to the upper pole of the kidney (7,8).

When a ureteral bud originates higher than normal on the mesonephric duct, it is incorporated into the urogenital sinus later than normal. This results in a shorter cranial and lateral migration, resulting in displacement of the ureteral orifice toward the bladder neck. If it originates very high, it might fail to be incorporated into the bladder altogether and end in the urethra or in the mesonephric remnants (i.e., epididymis, vas, seminal vesical, or Gartner's duct). Gartner's duct runs from the broad ligament of the uterus along the lateral wall of the vagina to end at the hymen. A ureter draining into this duct may result in secondary rupture of the duct into the vagina, creating a vaginally ectopic ureter. All ectopic ureters terminate above the level of the external urethral sphincter in the male, so that urinary incontinence is uncom-

mon. In the female, ectopic ureters may exit below sphincteric control, creating constant wetting from the ectopic ureter.

URETERAL DUPLICATION

The right and left kidneys are affected equally by ureteral duplication, and bilateral duplication occurs in about 40% of cases (9). Urinary infection is the most common associated finding, and in clinical series it occurs in females twice as often as males. In clinical series of patients with urinary symptoms, the incidence of duplication is from 2 to 4% (10). The incidence of childhood UTIs is increased with duplication, as might be expected with the increased incidence of reflux or obstruction in these patients. Histologically, the incidence of renal hypoplasia or dysplasia and pyelonephritic scarring is increased (2,11).

A ureteral bud that bifurcates early results in a partial duplication. A bifid renal pelvis is the result of the highest level of bifurcation and occurs in about 10% of the population. Of the other incomplete duplications, approx 25% divide in the proximal third, 50% divide in the middle, and 25% divide in the distal third of the ureter (Fig. 2). Most partial duplications are discovered incidentally; however, with a Y junction in the ureter, it is possible for urine to be passed down to the junction and then, in a retrograde fashion, up the other side of the Y (yo-yo reflux) (12,13).

When surgery is necessary for an incomplete duplication and the duplication is very low, a reimplantation of the ureters into the bladder with separate ureteral orifices may be possible (14). With a more proximal duplication, a ureteropyelostomy or ureteroureterostomy at the kidney level is curative (15). On occasion, ureteropelvic junction obstruction may be found in association with incomplete duplex systems (16). Usually the lower pole ureter is narrowed, and a side-to-side anastomosis of the obstructed lower pole pelvis to the upper pole ureter is required.

Fehrenbaker and colleagues found reflux in more than two-thirds of children with complete duplex systems who were seen because of a UTI (17). Intravenous pyelogram (IVP) and the voiding cystourethrogram (VCUG) establish the diagnosis by showing a duplex renal system with VUR. Reflux typically occurs into the lower moiety of a duplicated kidney drained by a ureter with a laterally ectopic ureteral orifice and a shortened submucosal tunnel (Fig. 3) (18). When the grade of reflux is low (I–II), it usually resolves spontaneously with growth of the child, avoiding the need for surgery (19,20). Surgical management may be more appropriate when the grade of reflux is high and the likelihood of

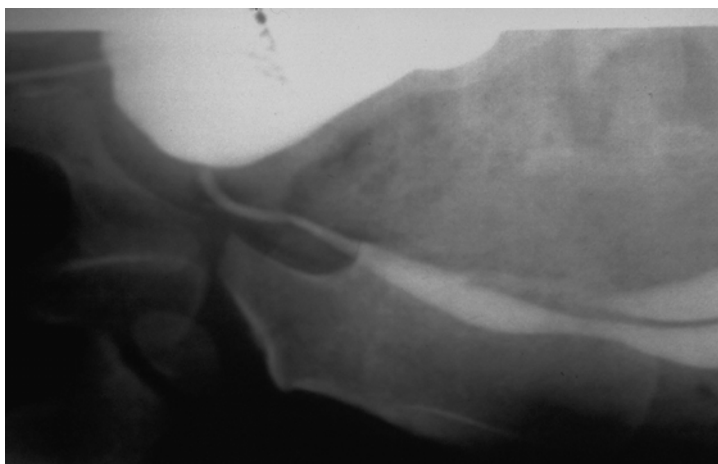


Fig. 2. Cystogram demonstrating reflux into incomplete duplication joining in the distal third of the ureter.

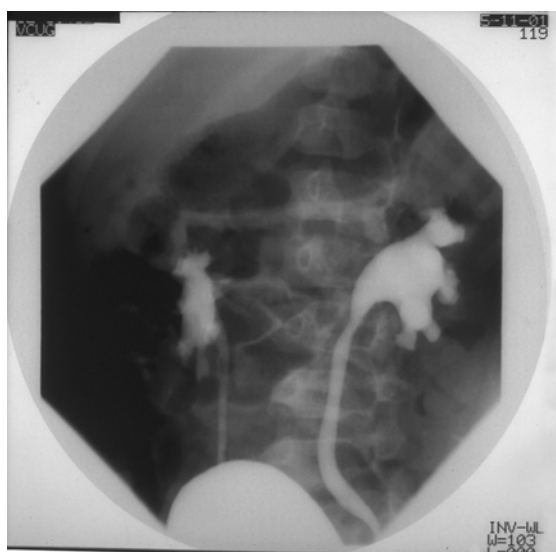


Fig. 3. Cystogram demonstrating bilateral reflux into lower poles of kidneys with complete ureteral duplication.

spontaneous resolution is small. In a complete duplication, the distal 2–3 cm of the two ureters is usually bound in a common sheath. Surgical correction involves mobilization and reimplantation of the common sheath, even though reflux has been observed in only one ureter (21,22).

URETEROCELES

The reported incidence of ureterocele is 1 in 4000 autopsies of children (2). Ureteroceles occur four to seven times more frequently in females than in males (23). There may exist a slight left-sided predominance of ureterocele, and about 10% are bilateral (24). Sixty to eighty percent of ureteroceles are ectopic (25–27), and about 80% are associated with the upper pole ureter of a duplex kidney (28). A single-system ectopic ureterocele is more likely to occur in males than in females (29). When the ureterocele arises from the upper pole of a duplex kidney, the upper pole frequently displays renal dysplasia (30).

Ureteroceles are most frequently found on prenatal ultrasound, although infection continues to be a common presentation after birth (31–34). Prolapse of a ureterocele may lead to bladder outlet obstruction, which constitutes the most common urethral obstruction in girls (35–37). Once a ureterocele is identified antenatally, follow-up ultrasounds are needed to assess for progression of obstruction over time. When tense, a ureterocele may obstruct the ipsilateral lower pole ureter or contralateral ureter as well as the bladder outlet. The presence of oligohydramnios and the gestational age of the fetus dictate the need for intervention. If gestational age is less than 34 wk, prenatal intervention is indicated for oligohydramnios. Minimally invasive techniques such as percutaneous ureterocele puncture should be the first-line management, with more invasive methods reserved for failure of decompression of the ureterocele. If gestational age is greater than 35 wk, delivery should be strongly considered because the risks of prematurity are minimal (38,39). Occasionally, a large ureterocele with an abnormal lax bladder neck may lead to incontinence before or after the ureterocele is surgically treated (40,41).

The diagnosis of a ureterocele relies predominately on ultrasonography (34,42–44). Ultrasound may demonstrate a well-defined cystic mass along the posterior bladder wall (Fig. 4A,B). Many ureteroceles are compressible with bladder filling, and ultrasonography done when the bladder is very full may miss the mucosal irregularity of the bladder base. There is often a dilated ureter behind the bladder that is also associated with the ureterocele (Fig. 4C).

A ureterocele associated with good renal function usually occurs with single-system intravesical ureteroceles. The majority of ectopic ureteroceles are associated with the upper pole of a duplex kidney that exhibits minimal or no function (Fig. 5) (33,45). In these cases, the signs of a ureterocele on an IVP are primarily negative, reflecting the displacement of the functioning lower pole and ureter by the hydroneph-

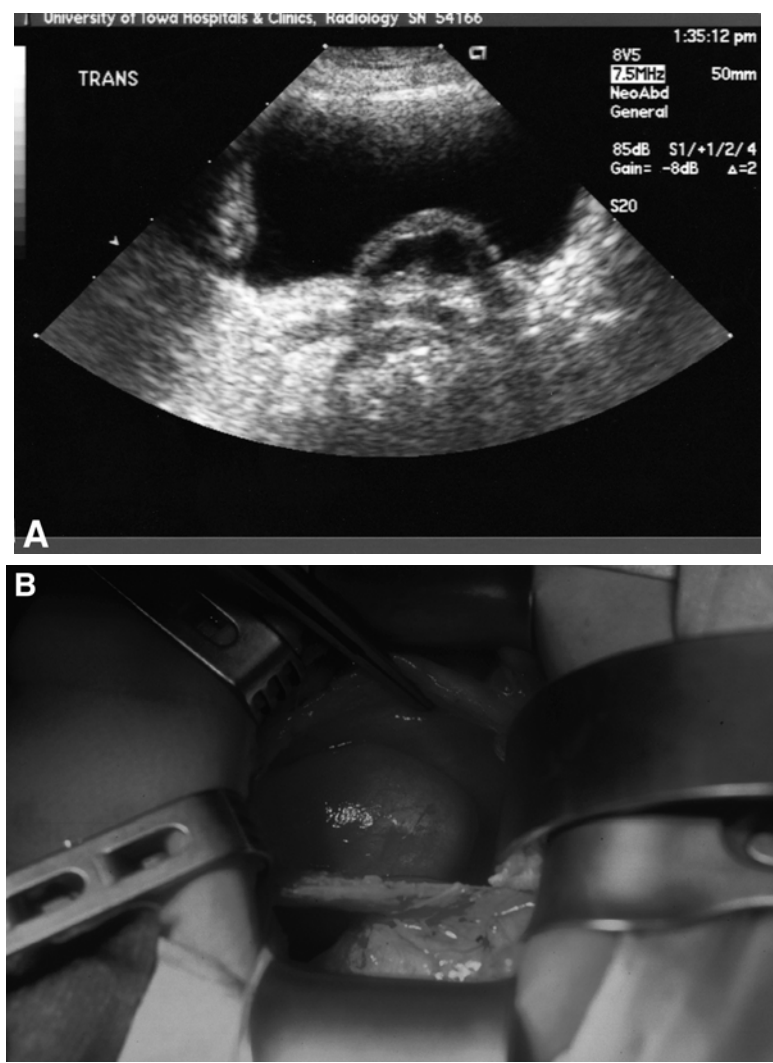


Fig. 4. (A) Large, thick-walled ureterocele demonstrated on ultrasound. (B) Intraoperative view of large intravesical ureterocele.

rotic upper pole. The lower pole renal unit is often downward and laterally displaced, producing the characteristic drooping lily sign. The lower pole ureter may be tortuous and displaced away from the spine as it wraps around the dilated upper pole ureter (Fig. 6). At the bladder level, a negative shadow may be seen and can vary from a large, tense, round shadow occupying much of the bladder volume to a minor irregu-



Fig. 4. (C) Ultrasound demonstrating dilated ureter behind bladder associated with a ureterocele.

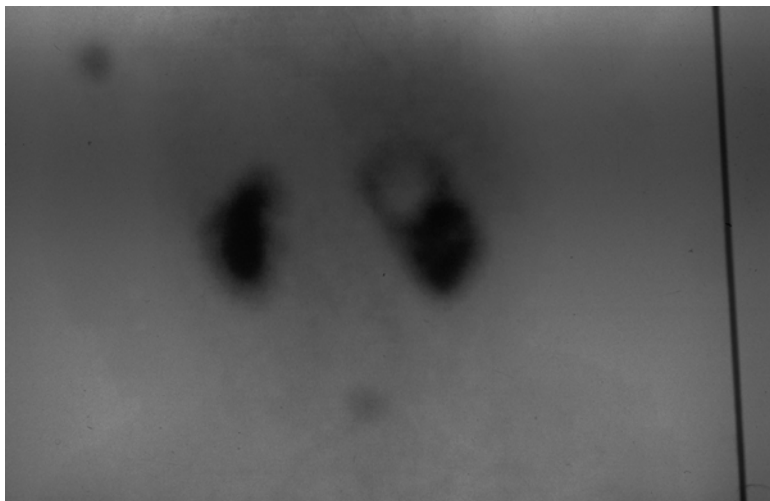


Fig. 5. Renal scan demonstrating rim of functioning renal parenchyma in right kidney associated with duplicated system and ectopic ureterocele.

larity along the floor of the bladder (Fig. 7). In a ureterocele associated with a duplex unit, especially if there is little hydroureteronephrosis, the diagnosis may be more difficult. The early films and the postvoid films from a urogram should be examined because, once the bladder is filled with contrast, the ureterocele may be obscured.

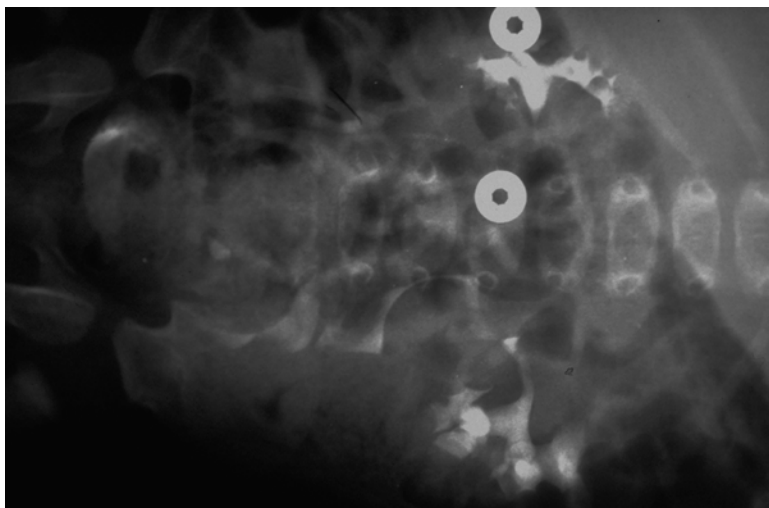


Fig. 6. IVP with a duplicated left upper pole ureterocele. The lower pole collecting system is displaced downward and lateral (drooping lily), and the lower pole ureter appears tortuous because of displacement from the unseen upper pole hydroureteronephrosis.



Fig. 7. IVP demonstrating large left intravesical ureterocele as a filling defect within the bladder.

A VCUG is a critical component in the evaluation of ureterocele. With duplex ureterocele, reflux occurs in the ipsilateral lower pole in about 50% of cases (28,33,45). In approx 25% of cases, there is contralateral reflux, and in about 10%, there is reflux into the ureterocele

itself (45,46). Reflux into a single system ureterocele can also occur (45,47). If detrusor support is poor and the ureterocele prolapses through the detrusor with voiding, the ureterocele may mimic a bladder diverticulum (48,49).

The cystoscopic examination of a ureterocele can be variable and confusing. A small ureterocele may not be apparent until a peristaltic wave or flank compression causes it to fill (Fig. 8A). A very large ureterocele may obscure the anatomy, making identification of any ureteral orifice impossible (Fig. 8B). A compressible ureterocele may come to resemble only a minor mucosal fold with bladder. When the ureterocele has poor detrusor support and prolapses, it may be misdiagnosed as a bladder diverticulum (50). These variables require the urologist to carefully inspect the bladder when it is empty and as it slowly fills. Because contralateral duplications are common with ureteroceles, the contralateral anatomy must be assessed during cystoscopy to avoid damaging a ureteral orifice that was not readily apparent. Occasionally, the dilated lower end of an ectopic ureter may elevate the trigone and give the appearance of a ureterocele (pseudoureterocele) by cystoscopy, ultrasound, or VCUG (51).

Treatment Options

The goals of ureterocele treatment are control of infection, protection of normal ipsilateral and contralateral units, preservation of renal function, facilitation of subsequent reconstructive procedures, and maintenance of continence. A number of factors must be considered when determining which treatment approach is optimal, and treatment must be individualized because no one approach is appropriate for all patients with ureterocele.

The age of the patient at the time of detection is an important factor in determining treatment. Because the natural history of asymptomatic ureteroceles is unknown, the effect of any treatment option on asymptomatic neonatal ureteroceles is difficult to determine. To further define the natural history of prenatally detected ureteroceles, one study followed 14 patients with ureterocele who did not undergo surgical intervention for a median of 8 yr (52). Reflux resolved in eight of the children during follow-up, and in six, mild hydronephrosis and collapse of their ureteroceles resolved. This study suggested that criteria for surgical intervention should include breakthrough UTI, upper pole function more than 10%, grade III or higher reflux affecting the lower renal pole, or bladder outlet obstruction. If surgical intervention is deemed necessary in an infant, an endoscopic incision has the advantage of providing a simple and direct decompression of the obstructive uropathy. An infant

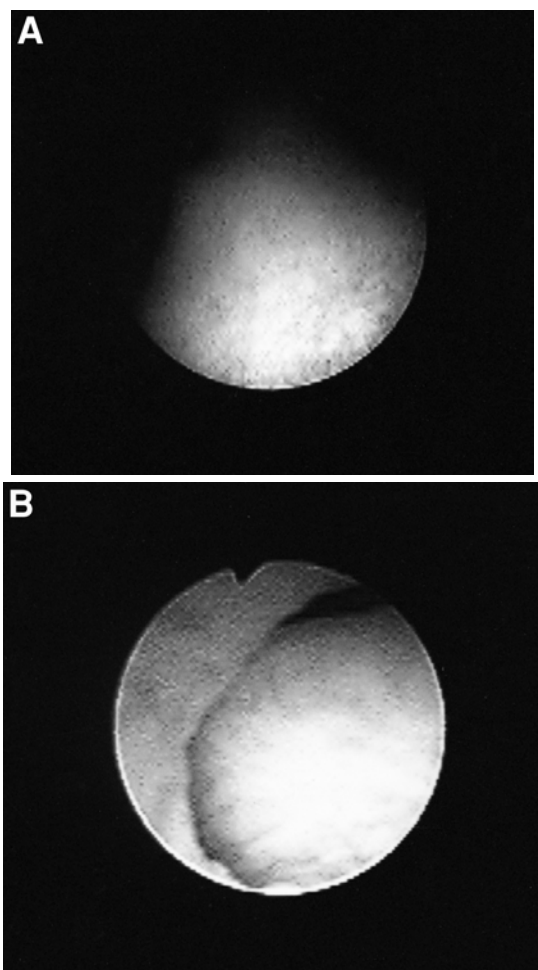


Fig. 8. (A) Cystoscopic image of a small intravesical ureterocele. (B) Image of a large left intravesical ureterocele, viewed from the urethra.

may tolerate this procedure better than a more complex upper pole partial nephrectomy.

After toilet training, bladder neck surgery such as ureterocele excision and bladder neck reconstruction causes a considerable degree of postoperative discomfort. This form of treatment would best be accomplished before toilet training. If a ureterocele is detected after toilet training, an upper pole partial nephrectomy may allow the patient to avoid bladder surgery; however, it may not be definitive because of associated reflux (33).

Renal function associated with the ureterocele is often considered in determining treatment, although the upper pole associated with the ureterocele typically makes up at most one-third of the renal function of one kidney (53). Often, infection or dysplasia decreases the amount of function to less than one-third of normal, and preservation of this tissue should not be a major factor in determining treatment. On the other hand, a poorly functioning renal unit drained by a decompressed ureterocele with no reflux does not routinely require removal.

An important factor in determining treatment is whether the kidney is single or duplex. In a single-system ureterocele, a primary endoscopic approach would almost always be appropriate because any open surgery would be directed at the bladder level. After endoscopic incision, one would have the advantage of reimplanting a smaller decompressed ureter should postendoscopic incision VUR require an open operation.

The degree of ureteral dilatation is important. On occasion, when there is a small ureter running to a small intravesical ureterocele, reimplantation of the ureter from the poorly functioning upper pole provides definitive treatment (54). If the ureter serving the ureterocele is massively dilated, reimplantation is more complicated. In this situation, an upper pole heminephrectomy may be appropriate. Alternatively, successful endoscopic decompression of a dilated ureter and ureterocele relieves obstruction, permitting a delay in further surgery, along with a decrease in ureteral dilatation and bladder enlargement and improved reimplantation results.

Associated VUR appears to best predict the need for open surgery. If high-grade reflux is associated with a ureterocele, a primary endoscopic incision facilitates subsequent reimplant surgery by decompression (34). If there is no VUR, then a simplified approach by an upper pole partial nephrectomy for an ectopic ureterocele is a reasonable treatment option. A review by Husmann showed that 60% of patients with less than grade III reflux in only one ureter did not require further surgery (41). In contrast, a higher-grade reflux into one or more renal moieties almost invariably led to further surgery (96%).

Consideration of the ureterocele as intravesical or extravesical is an important distinction, and the treatment options for each of these types of ureterocele will be discussed separately below. With extended follow-up, only 18% of patients with an intravesical ureterocele required a second operation after endoscopic incision, whereas 64% of patients with an extravesical ureterocele required a second operation (55). Prior endoscopic decompression of extravesical ureteroceles, however, should permit definitive surgery, using one incision at the bladder level,

with results approaching those seen for ureters without a ureterocele (i.e., greater than 90% success) (34).

Intravesical Ureterocele Treatment

Intravesical ureteroceles associated with a single ureter are more commonly seen in adults and older children (56). Single-system ureteroceles usually are associated with better function and less hydro-nephrosis than duplex renal units and ectopic ureteroceles. For single-system ureteroceles, a primary endoscopic approach is advisable in almost all cases. Even if reflux were to follow, the decompressed ureter would be easier to reimplant. More than 80% of patients with intravesical ureteroceles may be adequately treated by endoscopic incision alone (55,57).

The current approach to ureterocele decompression is to place a small puncture low on the ureterocele to preserve a flap valve of the collapsed ureterocele to prevent reflux. This approach was suggested by Monfort et al. (58,59) and by Blyth et al. (60). A 3-Fr Bugbee is used, and the cutting current ensures a clean puncture. If the ureterocele appears to be very thick-walled, a slightly larger incision may be appropriate (34).

Follow-up after an endoscopic incision initially involves a renal and bladder ultrasound 1 mo after the procedure. Although residual hydroureteronephrosis often persists, a diminution of some degree indicates that decompression has been achieved. Results of subsequent imaging of the upper tracts and VCUG direct further treatment.

If poor detrusor backing for the ureterocele is found during open reconstruction, the bladder wall must be repaired at the time of ureterocele excision. With significantly dilated ureters associated with ureteroceles, even following decompression, a tailored reimplant may be required. Cohen's technique of cross-trigonal advancement generally permits placement of the reimplant away from the area of bladder wall reconstruction (61).

When an intravesical ureterocele is associated with the upper pole of the duplex kidney, the upper pole often demonstrates poor function, and an upper pole partial nephrectomy and partial ureterectomy to below the level of the iliac vessels may be performed. This approach is particularly attractive when there is no VUR because it avoids bladder-level surgery (41). However, the incidence of VUR after endoscopic incision of intravesical ureteroceles is low, and an endoscopic approach remains a reasonable alternative in this situation as well.

An intravesical ureterocele as part of a duplex unit may be associated with adequate function and a ureter small enough (especially after

endoscopic decompression) to permit ureterocele excision and a common sheath reimplant of the two ureters. If there is no reflux driving surgery at the bladder level, and if upper pole function justifies salvage, a renal-level ureteroureterostomy or ureteral pyelostomy may also be used effectively.

Ectopic Ureterocele Treatment

Despite the frequent need for open surgery following an endoscopic approach for ectopic ureteroceles, the simplicity and minimal invasiveness of this technique is advantageous in neonates. If, as is common, associated reflux drives open bladder-level surgery, reconstructive surgery can be carried out electively when the patient is between 1 and 2 yr of age. At this time, complicated reconstructive procedures at the bladder neck are more safely accomplished and better tolerated than if they are postponed until after the age of toilet training. The decompressed ureter to the ureterocele can usually be successfully reimplanted, and upper pole partial nephrectomy, even for a poorly functioning upper pole, is rarely needed.

The traditional method of treatment of an ectopic ureterocele associated with a duplex renal unit was total reconstruction, with excision of the ureterocele, reconstruction of the detrusor, and reimplantation of the ipsilateral lower pole ureter and the contralateral ureter if required (62). A separate flank incision was made and an upper pole partial nephrectomy completed (63,64).

Most ureteroceles are now seen in the very young, and the total reconstruction approach requires a technically challenging excision of a large ureterocele, often with a urethral extension. Complications are not rare (65). A lip of the urethral extension of an ectopic ureterocele may act as a urethral valve and produce bladder outlet obstruction. In addition, if the ureterocele is excised but the bladder neck imperfectly reconstructed, incontinence may follow (40). Proponents of this approach note that most children may be treated with one operation, albeit with two incisions. In one series, only 14% of children with extravesical ureteroceles that underwent total reconstruction required subsequent intervention (66).

Because of potential complications resulting from a total reconstruction early in life, alternative treatments were developed. In duplex renal units with an associated ectopic ureterocele, the upper pole unit usually has not demonstrated sufficient function to warrant salvage (45,67). Because of this, a simplified approach, based on a primary upper pole partial nephrectomy with ureterocele decompression and later a staged approach to bladder-level surgery, was attempted at several institutions (33,68–70). The upper pole ureter was excised down to the level of the

iliac vessels and left open to facilitate decompression of the ureterocele. The expectation was that decompression would simplify bladder surgery that would be carried out when the child was older if reflux did not resolve. Husmann et al. noted that reflux developed in 30% of children without reflux following partial nephrectomy (71). Half of these children spontaneously resolved reflux and the other half required additional surgery for reflux. Other series suggest that the overall need for eventual bladder surgery ranges from 25 to 50% (33,69,70). The significant need for lower tract reconstruction has led some to suggest that, in older children, complete reconstruction may be a more definitive and efficacious treatment modality (71). The advent of the laparoscopic heminephroureterectomy presents another operative alternative that may be best selected in this group of children (72).

Salvage of the upper pole renal unit by a primary bladder-level operation involving excision of a nondecompressed ureterocele and a common sheath reimplant has the disadvantage of requiring the reimplant of an often very dilated ureter into the small bladder of an infant. Amar et al. suggested ureterocele excision, lower pole ureteral reimplantation, and a low ureteroureterostomy of the upper pole ureter into the lower pole ureter (73). Another alternative with obvious advantages is endoscopic decompression followed by an open operation at the bladder level when the child is between 1 and 2 yr of age.

When performing an upper pole partial nephrectomy, the upper pole renal vasculature is often anomalous and variable (74), and care should be taken to identify the small vessels that enter directly into the upper pole. No attempt is made to dissect out the hilar vessels. The ureter to the upper pole is divided, staying close to the upper pole collecting system so that vessels running to this unit can be clearly identified and divided. The upper pole of the kidney usually can be mobilized and rotated up into the incision.

As the vessels are tied, they form a line demarcating the devitalized upper pole. Often the division between the upper and lower poles is apparent before devascularization by a cleft in the parenchyma. The upper pole capsule is incised relatively high on the upper pole and may be stripped back for later use in closure. After the parenchymal incision is made just on the upper pole side of the line of demarcation from the lower renal unit, the upper pole can be excised. The upper pole ureter should be dissected down to below the level of the iliac vessels, where it enters a common sheath with the lower pole ureter. The upper pole ureter usually is tortuous and frequently appears to wrap around the lower pole ureter. Dissection kept immediately on the wall of the upper pole ureter should prevent injury to the lower pole ureter. If no reflux into the ureterocele is

noted, the stump of the excised upper pole ureter is left open. If reflux into the ureterocele is noted, the upper pole ureter should be ligated following aspiration of urine from the system.

During reimplantation following an upper pole partial nephrectomy, as the ureterocele is mobilized, the upper pole ureteral stump will be mobilized with the lower pole ureter. After the lower pole ureter has been sufficiently mobilized for an adequate reimplant, the upper pole ureteral stump is opened on its wall opposite the common one shared with the lower pole ureter. No effort is made to excise the portion of the wall of the upper pole ureter that is contiguous with the lower pole ureter to minimize the risk of injury to the lower pole ureter. A Cohen cross-trigonal reimplant is usually feasible and keeps the course of the ureter away from the area of recent bladder wall reconstruction.

If the treatment choice involves excision of the ureterocele and bladder neck reconstruction, the surgery should be done before the age of toilet training. There are two basic methods for the intravesical excision of a ureterocele. If the detrusor backing for the ureterocele is solid, the back wall of the ureterocele can be left in place. However, a bladder wall reconstructive procedure is warranted if there is detrusor weakness behind the ureterocele. If the ureterocele has a urethral extension, the surgeon must not leave a distal lip of mucosa that can be an obstructing valve.

To reconstruct the bladder neck defect after ureterocele excision, the technique of keeling, as described by Boijsen, is particularly attractive (74).

A series of sutures is used to evert the detrusor posteriorly (keeling) until the bladder neck is reconstructed to a normal diameter. The mucosal edge of the ureterocele provides a good guide as to the amount of eversion needed.

ECTOPIC URETER

Ectopic ureters terminate in multiple sites in both males (always above the sphincter) and females. The incidence of ectopic ureters is 1 in 1900 births, and it occurs in females 85% of the time (2,75). In 80% of cases, the ectopic ureter is attached to the upper pole of a duplicated kidney. The percentage of ectopic ureters associated with duplication in females is higher than 80%, with single-system ectopic ureters occurring more frequently in males (76,77). The incidence of bilateral ectopic ureters approaches 10% (78). With a duplex ectopic ureter, contralateral duplication occurs in about 80% of cases, and 21% of these also have contralateral ectopy (79).

In general, the degree of ectopia correlates with the degree of renal abnormality. This correlation is more apparent for duplex systems with

ectopy than for single systems with ectopy (80). Severe ectopia with an orifice in the genital system is almost always associated with nonfunctioning renal tissue (75,81). When two single ureters are ectopic, the bladder neck fails to form normally, resulting in incontinence (82).

Ectopic Ureter in the Female

The fundamental difference between ureteral ectopia in the female and in the male is that in females ectopic ureters can terminate at a level distal to the external sphincter and cause incontinence (83,84). About one-third of ectopic ureters open at the level of the bladder neck or slightly more distally in the upper urethra (85). An orifice inserting more proximal along the bladder neck and urethra has a smaller chance of causing incontinence; however, obstruction is more common because the more proximal ureters traverse a greater portion of the musculature of the bladder neck. These more proximal ectopic ureters drain only during voiding when the bladder neck muscles relax. VUR occurs in 75% or more of these higher ectopic ureteral orifices, producing the paradox of both reflux and obstruction. By having the bladder neck repeatedly open during a multiple-cycle VCUG, the obstructed ectopic ureter may drain before contrast is voided, increasing the likelihood that the contrast will reflux into the ectopic system (Fig. 9) (86). Reflux is less common when the ectopic ureter enters at the level of the external sphincter or more distally.

In females, one-third of ectopic ureters terminate in the area of the vaginal vestibule immediately around the urethral orifice. Occasionally, an ectopic ureter enters what appears to be a urethral diverticulum or anterior vaginal wall mass but what is actually a Gartner's duct cyst (87). About 25% of ectopic ureters enter into the proximal vagina. More rarely, an ectopic ureter can end at a higher site on Gartner's duct, with an opening at the level of the cervix or even the uterus (< 5%).

About half of females with ectopic ureters have a classic history of continuous dribbling incontinence despite what appears to be a normal voiding pattern (75,79,80). Occasionally there is a persistent foul-smelling vaginal discharge. When the ectopic orifice is quite high and there is significant obstruction, reflux, or both, urinary infection is frequent and is the most common reason that parents of small children seek treatment. An infant may have an abdominal mass resulting from a severely obstructed ectopic ureter (88). Not all ectopic ureters entering the vestibule or distal urethra cause incontinence, which may be the result of obstruction of the ureter as it traverses the continence mechanism (89).

The diagnosis of an ectopic ureter in the female may be very difficult. With ectopy into the external genitalia, the associated renal unit may not



Fig. 9. VCUg demonstrating reflux into lower pole ureter associated with right upper pole ectopic ureter. Note displacement of upper pole collecting system and ureter.

be seen (90). Ultrasound may be especially useful in detecting the dilated ectopic ureter behind the bladder (Fig.10). If there is little hydronephrosis of the ectopic upper pole system, diagnosis may depend on recognizing the absence of an upper pole calyx or an apparent excessive thickness of the renal tissue on the medial aspect of the upper pole. Tomography during urography or a computed tomography image of the kidney may aid in making this diagnosis (Fig. 11) (91). Magnetic resonance imaging (MRI) has been used to delineate the fluid-filled ureter and its anatomy (92). Bilateral ectopic ureters occur in about 10% of cases, and diagnosis frequently requires a high index of suspicion.

Physical examination with close observation of the area around the urethral meatus and distal vagina may reveal a recurring drop of liquid over a very small opening that can be probed and reinjected to confirm the presence of an ectopic ureter. The presence of an ectopic ureter may be suggested if observation of the perineum reveals a continued slow drip of clear urine after filling the bladder with indigo carmine- or methylene blue-stained saline by means of a Foley catheter. Phenazopyridine hydrochloride (pyridium) appears to be a better color marker to be excreted by poorly functioning renal tissue than methylene blue or indigo carmine (93) and thus, if a cotton swab is left high in the vagina overnight and is stained orange, it may suggest the diagnosis of a vaginally ectopic ureter. Vaginoscopy with attention to the superior lateral aspect of the vagina may reveal vaginal ectopia.

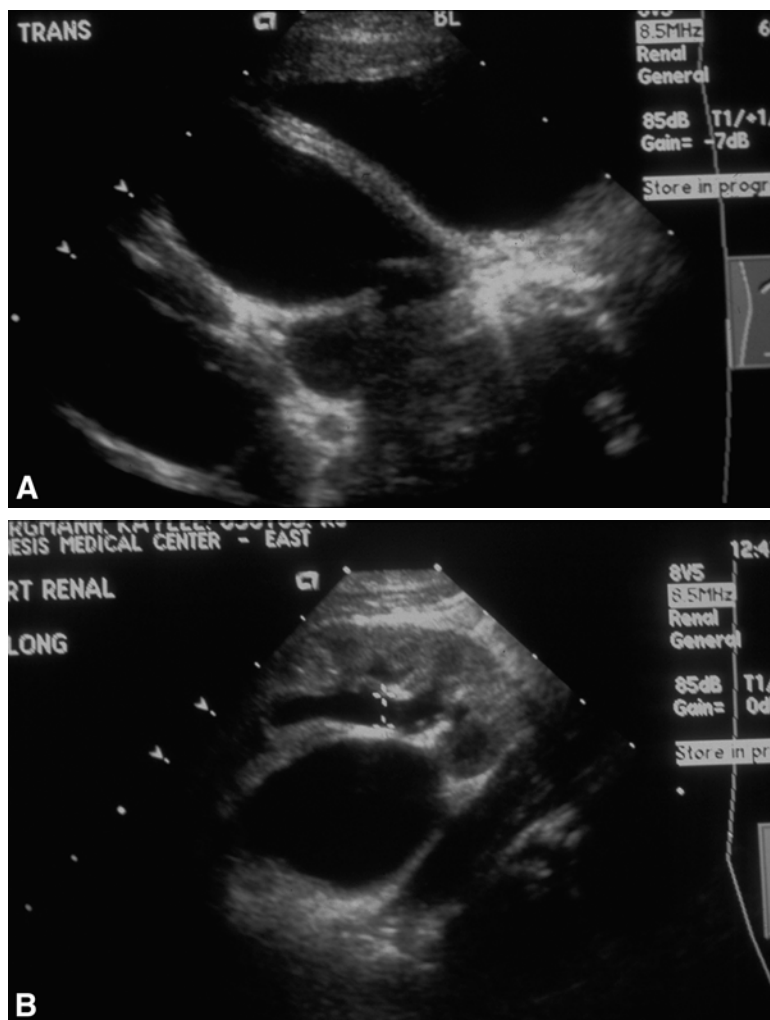


Fig. 10. (A) Pelvic ultrasound demonstrating massively dilated ectopic ureter posterior to bladder. (B) Renal ultrasound in same patient demonstrating severe hydronephrosis of upper pole and mild hydronephrosis of lower pole.

The surgical treatment of an ectopic ureter in a female depends on the associated renal function. Single-system ureteral ectopia to the genital system usually has poor function, and a nephroureterectomy is appropriate. With single-system ectopia to the bladder neck or urethra, the function may justify a reimplantation of the ureter into the bladder (80). When the ectopic ureter is associated with the upper pole of a duplex renal unit, function of the upper pole is usually poor, and a partial

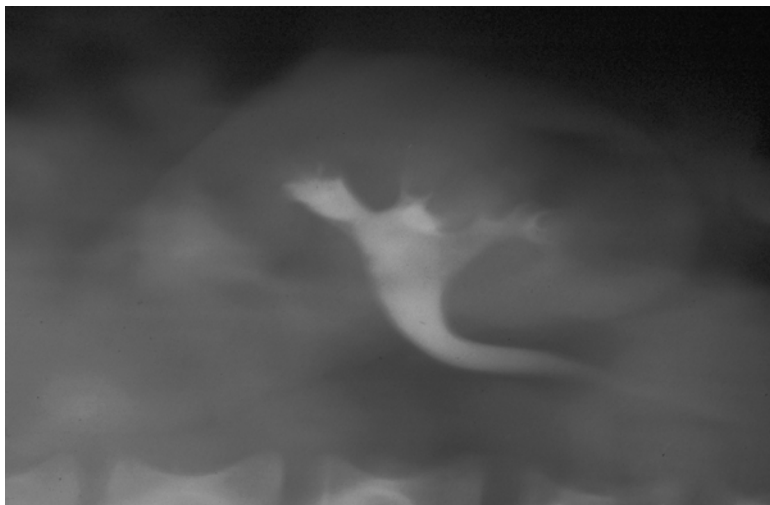


Fig. 11. IVP demonstrating increased renal tissue along the upper medial pole consistent with ureteral duplication.

nephroureterectomy is performed. Rarely, the upper pole functions enough, and a ureteropyelostomy or ureteroureterostomy to drain the ectopic system into the lower pole system is appropriate. If the lower pole pelvis is intrarenal and the lower pole ureter is not dilated, this approach is less feasible. The ectopic ureter can be reimplanted into the bladder, although it is usually sufficiently dilated to warrant tailoring.

If an ectopic ureter enters into the introitus or vagina, the entire distal ureter does not usually need to be removed. The distal ureteral segment is a rare source of later problems (80,94). If the distal segment becomes a source of stasis and infection, marsupialization of the ureter, usually a Gartner's duct cyst, into the vagina will correct the problem. If there is an ectopic ureter ending in the bladder neck or urethra, then reflux of voided urine into the residual ureteral stump is likely to occur. This may lead to a small amount of dribbling incontinence after micturition or recurrent urinary infection. Thus, removal of the ureteral stump is more likely to be needed for urinary ectopic ureters.

Ectopic Ureter in the Male

Ectopic ureters in the male may end in the bladder neck, in the posterior urethra to the level of the verumontanum, and in the mesonephric duct derivatives (epididymis, seminal vesicle, and vas deferens). One-half of male ectopic ureters end in the posterior urethra (78) and more than one-third join the seminal vesicle (95,96). Ectopic ureters to the male

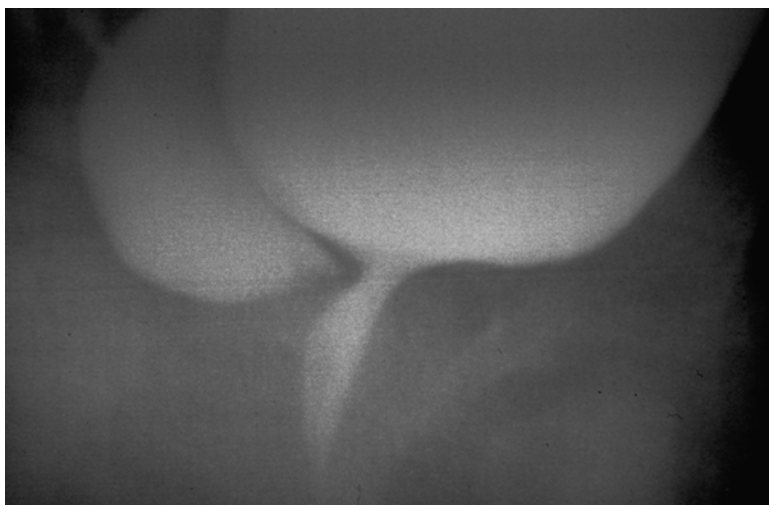


Fig. 12. VCUG demonstrating reflux into dilated ectopic ureter inserting into urethra.

genital tract may be seen as epididymitis. Accordingly, any prepubertal male with epididymitis requires evaluation for an ectopic ureter (97).

Because ectopic ureters in the male enter above the external sphincter, they generally do not produce incontinence. Symptoms of flank pain and urinary infection are more common. A dilated single-system ectopic ureter into the prostatic urethra may elevate the bladder neck, causing obstruction (98).

A high index of suspicion may be required to diagnose an ectopic ureter in the male. An ectopic ureter entering the genital tract is often single and drains a nonfunctioning renal unit (81,93,99). Ultrasound may demonstrate a dilated ureter and its associated renal element; however, diagnosis is very difficult when there is a tiny upper pole unit draining into a minimally obstructed ectopic ureter with little dilatation (100).

Most ureters ectopic to the urethra or bladder neck will reflux (80) and use of the cyclic voiding technique may enable the diagnosis to be made (Fig. 12). In the male as in the female, ectopic ureters at the level of the sphincter may demonstrate the paradoxical finding of both obstruction and reflux. MRI may be useful for diagnosing and demonstrating the ectopic ureteral anatomy (101). The advent of fast-scan MRI technology should improve the usefulness of this diagnostic study in the pediatric population.

Cystoscopy and examination with the patient under anesthesia are useful in establishing the diagnosis (Fig. 13). A mass may be felt in the area of the seminal vesicle, or elevation of the floor of the bladder over

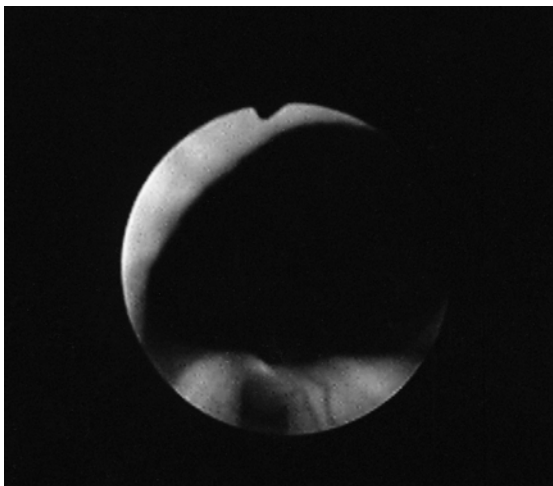


Fig. 13. Cystoscopic image demonstrating right ectopic ureteral orifice at level of bladder neck.

a cyst (pseudo-ureterocele) may be noted at cystoscopy. The ectopic ureteral orifice may be identified, or there may be an enlarged ejaculatory duct permitting a retrograde study that will establish the diagnosis. When there is single ureteral ectopia, a hemitrigone is present.

Treatment of ectopic ureters associated with duplex units in the male usually involves removal of the associated poorly functioning renal unit. Rarely, function is adequate to justify a ureteropyelostomy or ureteroureterostomy. Because the ectopic ureter is usually dilated, a reimplantation of the duplex ectopic ureter into the bladder is a less attractive alternative.

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9

Voiding Dysfunction

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INTRODUCTION

Voiding dysfunction is a term used to describe a constellation of problems that interfere with efficient storage and evacuation of urine. Symptoms may include recurrent bladder infections, day and/or night wetting, urgency, frequency, urinary dribbling, infrequent voiding, weak or intermittent stream, and/or straining to void. Sometimes referred to as dysfunctional elimination syndrome (DES), or nonneurogenic neurogenic bladder, this disorder causes significant distress to both health care providers and patients (1).

PREVALENCE

Voiding dysfunction is a common problem affecting children over the age of 4 yr and accounting for a large proportion of referrals to pediatric urologists. Children with voiding dysfunction are at risk for recurrent urinary tract infections (UTIs), vesicoureteral reflux (VUR),

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trophic changes to the bladder, urinary calculi, nocturnal enuresis, and hydronephrosis (2). There is a high incidence of psychological morbidity associated with voiding dysfunction (3). Furthermore, if left untreated, voiding dysfunction can worsen, ultimately resulting in surgeries that could have been prevented and/or progression to renal failure.

The incidence of voiding dysfunction is approx 10% in children between the ages of 4 and 6 yr. The incidence steadily decreases to 5% in children 6 to 12 yr old and is 4% in adolescents. The problem is more common in females than in males (13.3 vs 9.9%, respectively) (4).

Most children with dysfunctional elimination have no neurologic findings or anatomic obstruction (5). Instead, delayed or disturbed voluntary control of the bladder or the pelvic floor musculature is often implicated.

The physiologic changes that occur in dysfunctional voiding can be separated into two categories: filling phase dysfunction and voiding phase dysfunction. Filling phase defects are characterized by detrusor hypertrophy (trabeculated thick-walled bladder or diverticuli) that alters the closure mechanism at the vesicoureteral junction creating VUR. The bladder neck opens during an unstable contraction and urine is pushed into the urethra. Once the contraction abates, urine returns from the proximal urethra into the bladder, carrying with it bacteria that creates an environment for recurrent episodes of cystitis.

Dysfunction during the voiding phase is often conceptualized as a learned behavior that results from the child's attempt to suppress impending or active bladder contractions by inappropriately contracting the urethra and the pelvic floor muscles rather than relaxing during voiding. The resulting pattern is a cycle of increased voiding pressures or detrusor-sphincter dyssynergia that produces inefficient voiding (6,7). Symptoms include a rhythmic pattern of voiding known as staccato voiding, which is characterized by bursts of pelvic floor activity. The result is a peak in bladder pressure that coincides with interruption of urine flow.

The causality of the relationship between incontinence, UTIs, and VUR is not clear, although it has been suggested that UTIs early in life may play a role in the cause of DES (8,9). The reflux associated with voiding dysfunction may actually be a secondary problem. The reflux takes place under high-pressure conditions created when an unstable bladder contracts and anatomic changes occur related to detrusor overactivity. Hoebeke et al. (10) reported a 34% incidence of UTI in children with dysfunctional voiding. In contrast, Shaikh et al. (11) compared the incidence of voiding dysfunction in two cohorts of children with and without UTI diagnosed before age 2 yr. Within the UTI

cohort, 18% of children with documented VUR were positive for symptoms of DES compared with 25% without documented VUR. DES was reported in 22% of the children with UTIs and in 21% of the children without UTIs, suggesting that there is no causative association between DES and either UTI or VUR. Females are at a higher risk for developing UTI than males because females have a short urethra, creating a short distance between the perineum and bladder. The urge syndrome is also thought to have a causal relationship with dysfunctional voiding symptoms such as detrusor-sphincter dysynergia (12).

ASSESSMENT AND DISCUSSION OF PROBLEM

Bladder Physiology

The physiology of micturition involves sympathetic autonomic nervous system stimulation that leads to relaxation of the detrusor muscle and increased tone in the trigone muscles of the bladder neck and proximal urethra during bladder filling. Concurrently, somatic nerve stimulation via the pudendal nerve increases tone in the striated muscle component of the external urinary sphincter complex to prevent leakage. During voiding, sympathetic stimulation ceases, the bladder neck relaxes, and the detrusor muscle contracts (13).

The lower urinary tract can be conceptualized as consisting of the bladder (smooth muscle) and the sphincter (striated muscle). There is a transitional zone between the smooth muscle of the bladder and the urethral sphincter to create a functional sphincter. The lower urinary tract is dependent on the central nervous system and involves autonomic activity as well as voluntary control. Bladder function can be described as urine storage and elimination at a socially acceptable time and place. Bladder storage requires that increasing volumes be accommodated at a low intravesical pressure with appropriate sensation, that the bladder outlet remain closed during increased intraabdominal pressure, and that there be no voluntary contractions (14).

Symptoms of Voiding Dysfunction

Diurnal enuresis is classified as primary when a child continues to wet beyond the usual age of toilet training (4 yr) and as secondary if the child has had at least 3 consecutive months of continence followed by day incontinence (15,16). The usual symptoms associated with this type of incontinence may include bladder instability, including urgency, frequency, infrequency, and elevated postvoid residuals. Urge symptoms seem to peak between the ages of 6 and 9 yr and diminish toward puberty, with an assumed spontaneous cure rate for day wetting of about

14% per year (17). Urinary frequency is present in approx 20 to 30% of children with day wetting; however, most children with symptoms of frequency also have associated problems with urgency. Urgency is described as daily episodes of sudden urge that is often controlled by heel-sitting (squatting) or other posturing or bracing to avoid urinary leakage.

Symptoms of constipation or fecal soiling often coexist with the urinary symptoms (18), but are easy to miss because urinary symptoms can overshadow bowel problems. Parents tend to be less aware of their children's bowel habits as age and independence prompt the children to seek privacy in the bathroom. Although a parent will often deny that the child has bowel problems, a more in-depth clinical history often reveals a different picture. In fact, a prevalence rate for constipation of 30% was recently reported in a sample of children with voiding dysfunction (19).

Several theories have been suggested to explain the functional relationship between constipation and enuresis. The presence of a full rectum may lead to decreased bladder capacity and uninhibited bladder contractions caused by pressure from the rectum on the posterior bladder wall. The bladder is displaced and the urethra elongated, resulting in impaired bladder emptying (19). More likely, there is a reflex relationship that explains the effect of a full rectum on bladder and pelvic muscular activity.

PATIENT EVALUATION

History and Physical Examination

A complete history, including urinary and gastrointestinal (GI) symptoms is obtained. The onset and duration of symptoms, incidence and timing of accidents, evidence of frequency and/or urgency, and presence or absence of infection will help determine the complexity of the problem. Additional information includes a voiding diary documenting frequency and/or volume voided and a psychological profile of the child. The physical examination seeks to rule out obvious developmental or anatomic problems of the urinary, GI, and neurologic systems. A brief neurologic examination should assess for irregularities of the lumbosacral spine, and problems with perianal wink reflex, rectal tone, and perianal sensation. Fecal soiling or a full rectal vault should raise one's suspicions about constipation or encopresis.

Urinalysis and Culture

All patients should have a urinalysis to assess for the presence of protein or glucose in the urine, which requires further evaluation. UTI and asymptomatic bacteriuria are common findings and can impact bladder behavior. Bacterial counts more than 10^5 colony-forming units

of a single organism from a specimen obtained by clean catch midstream is considered a positive urine, and the appropriate antibiotic should be prescribed. Children who experience recurrent infections (<3 episodes of infection in 1 yr) should be considered for prophylactic antibiotics, although aggressive management of voiding dysfunction is preferred long-term.

KUB

KUB is a useful tool in assessing the degree of constipation and identifying other dense abnormalities such as kidney and bladder stones or spinal abnormalities (Fig. 1).

Renal and Bladder Ultrasound

Ultrasound studies are used to assess for the presence of hydronephrosis, hydroureter, and other anatomic abnormalities of the kidneys and bladder. It is also helpful in evaluating the thickness of the bladder wall and presence of a postvoid residual (PVR).

In addition to a formal radiologic ultrasound, a smaller portable ultrasound can be used to assess PVR as a part of the clinic evaluation and ongoing treatment of urinary retention (2,20). Residual urine is defined as the volume of fluid remaining in the bladder immediately after the completion of micturition. Residual volumes of more than 20 mL or more than 10% of expected capacity are considered clinically significant if documented on more than one occasion (15).

Voiding Cystourethrogram (VCUG)

Indications for a VCUG include nonfebrile UTI in a child less than 5 yr of age, febrile UTI regardless of age, and male children with a UTI. This study is performed after an initial UTI to identify VUR or other congenital anomalies of the lower urinary tract. Cystourethrography testing is performed under fluoroscopic control. A scout film is obtained before the test and can be useful in ruling out anatomic abnormalities such as spina bifida occulta.

Retrograde filling with a contrast solution allows for visualization of the bladder and ureters before, during, and after voiding. In addition to reflux, a finding such as spinning top urethra may be seen, which is considered an indication of habitual high-pressure voiding because of poor pelvic relaxation. (Fig. 2)

Complex Uroflow with Electromyography (EMG)

Coordination between the bladder and sphincter muscles is necessary to achieve low-pressure voiding and encourage complete bladder emp-



Fig. 1. Abnormal abdominal radiograph demonstrating a large amount of stool in the rectosigmoid.

tying. If there is voluntarily contraction of the pelvic floor muscles at the time of detrusor muscle contraction, urethral resistance is increased. This not only makes complete emptying more difficult, but it also requires higher pressures to complete the void. Eventually, the bladder becomes irritable and unstable. The complex uroflow demonstrates coordination between bladder and sphincter and is commonly used to assess for sphincter dyssynergy.

Flow EMG measures voiding time, volume, flow rate, and time to maximum flow. Surface EMG (sEMG) monitors electrical activity associated with contraction of the skeletal component of the external sphincter. The sEMG patches are placed at the 3 and 9 o'clock positions on the perineum. Normal urinary flow rates for children are reported at 15 mL/s (21). A normal flow-void pattern is characterized by a bell-shaped curve. A flattened curve or staccato spikes accompanied by increased sEMG activity are two of the most commonly seen aberrant patterns in young people with voiding dysfunction (Fig. 3).



Fig. 2. VCUG with a spinning top urethra, suggesting bladder-sphincter discoordination of a longstanding nature.

Urodynamics

Urodynamics are rarely needed in children with nonneurogenic voiding dysfunction. Urodynamic testing measures the relationship between pressure and volume of the bladder. This study evaluates bladder filling, detrusor activity, rectal activity, internal and external sphincter activity, urinary flow, and efficiency of emptying, and assess urinary leakage. In children, bladder filling pressure is usually less than 30 cm H₂O. In older children who have completed toilet training, the suppression of EMG activity of the pelvic floor muscles is the first event of the micturition cycle and occurs before detrusor contraction by a few seconds. Chandra et al. studied urodynamic outcomes in 70 infants with a history of UTI and 40 with concomitant VUR (22). Urodynamic dysfunction was iden-

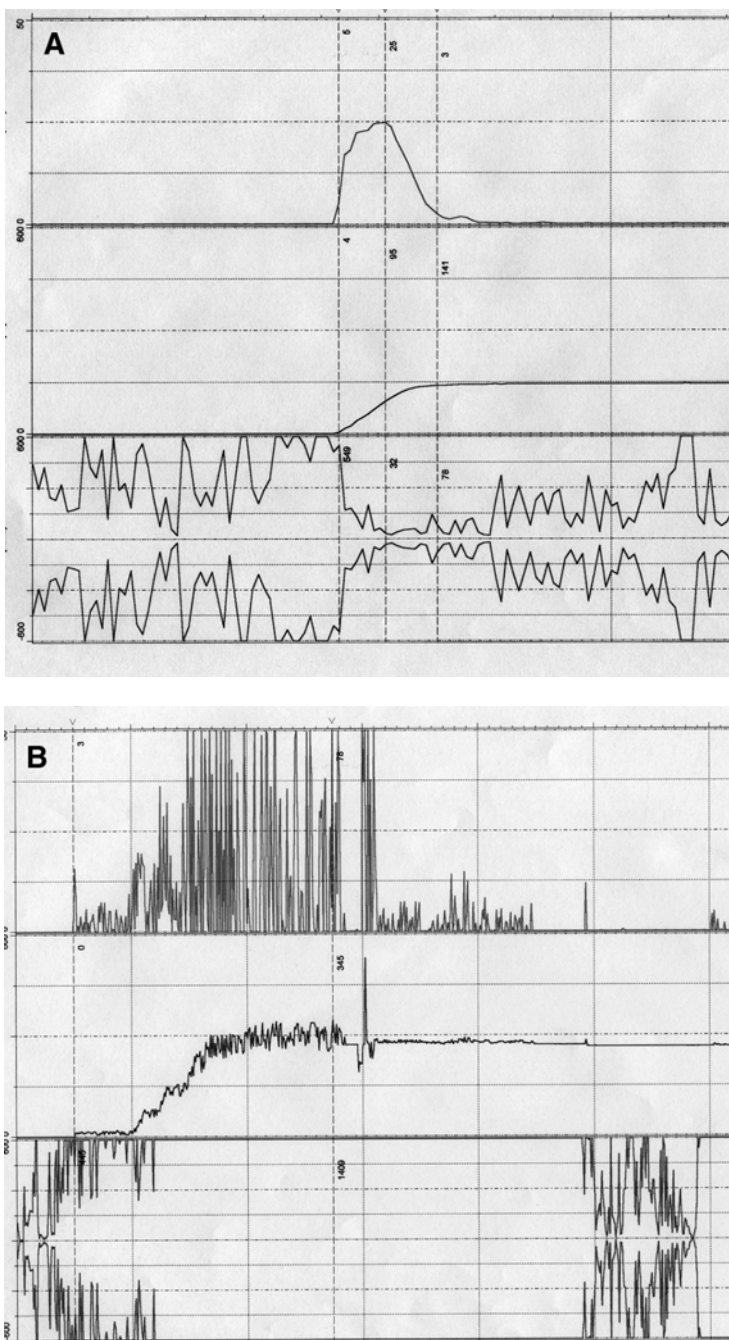


Fig. 3. (A) Normal complex uroflow and sEMG with a bell-shaped curve and decreased electrical activity of the sphincter during voiding. (B) Abnormal uroflow with a saw-toothed curve and significant EMG activity during voiding.

tified in 97% of male infants and 77% of female infants who had a voiding detrusor pressure more than 40 cm H₂O, reflex detrusor contractions during filling, and incomplete bladder emptying. In a subsequent study, Chandra and Maddix evaluated the urodynamic function of infants with primary VUR without UTI (23). Urodynamic dysfunction was found in 79% of the infants with VUR. In addition, 25% of the infants were found to have high voiding detrusor pressures more than 70 cm H₂O and PVRs indicating incomplete bladder emptying. Similarly, Yeung et al. found that infants with VUR had abnormal high detrusor pressures on urodynamic studies compared with controls (24). The elevated intravesical pressures may contribute to the development and severity of VUR. Mayo and Burns compared urodynamic studies in 187 children diagnosed with incontinence (25).

Children with unstable bladders (unstable filling phase but coordinated emptying) and those with dysfunctional voiding (unstable filling and emptying phases) were found to have high vesical pressures. Of note, children with symptoms of dysfunctional elimination had an increased incidence of encopresis, UTI, thickened bladder wall, reflux, and PVRs.

MRI

A lumbosacral MRI to rule out spinal cord abnormalities may be indicated if the neurologic examination is abnormal or if urodynamics, VCUG, or ultrasound suggest a neurogenic bladder. If there is any question about neurologic issues, a pediatric neurologist should be consulted.

Behavioral Characteristics

DEVELOPMENTAL CONSIDERATIONS

Extended periods of bladder and bowel continence usually occur between ages 2.5 and 3 in both well and chronically ill children. It is important to consider signs of physiologic readiness as well as factors specific to the child's condition that may impact on the child's success at obtaining day and night time continence. Children who lack sensation or who have never voided or had a stool because of an ostomy may experience delayed toileting. In addition, children who have experienced pain during urination or defecation may exhibit avoidance behavior when toilet training occurs.

SEQUELLAE OF VOIDING DYSFUNCTION

Children have reported that incontinence has resulted in experiences ranging from social isolation to physical and verbal punishment (26). Investigators have suggested that daytime and nighttime incon-

tinence may produce psychological and interpersonal distress that results in lower self-confidence and limits opportunities to participate in activities with peers (27,28). In a study of day and night incontinence, Hagloff et al. found that incontinence was associated with lower self-esteem (3). In addition, they found improvements in self-esteem with treatment. In a large-scale epidemiologic study, Ollendick et al. sampled 2000 children and adolescents to rank their concerns about stressful life events (29). The results indicated that wetting in class was the third most stressful event, behind loss of a parent and going blind. In a similar study, van Tijen et al. compared the perceived stress of diurnal enuresis in children with and without nocturnal enuresis (30). Children with a history of nocturnal enuresis ranked bedwetting as three (primary school age) and two (adolescents) as a stressful life event in contrast with controls, who attributed minor significance to the issue ($p < 0.001$). Other critical life events were ranked similarly between children with incontinence and those without. Often children with enuresis are labeled, teased by their peers, or punished by parents or other adults.

It is also important to mention that for children with a history of day or night wetting, their wetting behavior may act as a negative feedback mechanism, reinforcing their failure to achieve dry episodes. Frequently, a history of unsuccessful attempts at treatment cause children to refuse to participate in a voiding program or to participate with only a half-hearted effort (31).

It is readily acknowledged that there is controversy about whether psychological disturbances are a causative factor or consequence of enuresis (diurnal or nocturnal). Predisposing factors associated with daytime incontinence include family history, female gender, and a recent history of emotional distress (32). A recent report by Gerson et al. evaluated the incidence of behavior and emotional problems in a group of children in two voiding dysfunction programs (33). They found that although there was a slightly higher-than-expected incidence of several behavior disorders in the group, most of the children did not show evidence of severe behavior or emotional problems.

In another study, Von Gontard et al compared the incidence of behavior problems in children with urge incontinence (UI) and voiding postponement (VP) (26). No differences were found in the two groups with regard to internalizing behaviors. Children with VP were found to have significantly more clinical externalizing behavior problems ($p < 0.01$), most notably conduct disorders (refusal to obey rules, disruptive behavior in the classroom, and sibling rivalry). The authors concluded that VP

is a subsystem of oppositional conduct disorder. Although emotional problems are frequently found in children with UI, the authors suggest these are secondary to the wetting. The authors suggested that older children (< 8 yr) and those with more complex dysfunctional voiding patterns have a higher rate of behavior problems. In addition, they found that the characteristics most often associated with behavior problems in children with dysfunctional elimination include age more than 8 yr, daytime and nighttime wetting, higher frequency of wet episodes, and secondary vs primary enuresis.

The impact of day and night wetting on the family cannot be underestimated and often is reflected in behavior to seek medical assistance or independently manage the problem. Sureshkumar et al. studied the prevalence of daytime wetting in primary school children and found that only 16% of the families with children with daytime incontinence sought help (32). Parents of children who wet more frequently or who had symptoms of urgency were more likely to seek medical attention. However, only 40% of families whose children wet every day discussed the issue with their health care provider. Parental response may vary from disappointment, embarrassment, and anger to verbal or physical punishment. Dobson found that bedwetting is the second most common reason for nonaccidental injury in children, after persistent crying (34).

TREATMENT

Conservative treatment approaches rely on treating symptoms of voiding dysfunction with timed voiding programs and medications. When these fail, multicomponent and multidisciplinary treatment interventions that include medical and behavioral management are recommended to correct inefficient bladder habits, uncoordinated sphincter activity, and bladder storage problems. Integral to all types of treatment is developmentally appropriate education and psychological support that reinforces progress rather than cure and encourages long-term behavior change.

The anatomic proximity of the bowel and bladder outlets as well as the shared nerve innervation from the sacral plexus makes joint treatment of bowel and bladder dysfunction a necessity. Because the effects of medication and behavioral therapy alone or together are not completely satisfactory, biofeedback has become an important adjunctive treatment used in many clinics (35). Successful management of voiding dysfunction also requires parental and child motivation and compliance with the recommended treatment regimen.

Medical Management

PHYSICAL ASSESSMENT

Each session during treatment should include a physical examination to assess for flank pain, a palpable bladder, and constipation or palpable stool. A perineal assessment may reveal skin excoriations and fecal staining or wet pants that corroborate the history of progress made.

PHARMACOLOGIC AGENTS

Voiding dysfunction in children principally involves the lower urinary tract. Therefore, pharmacologic intervention is directed specifically toward the smooth muscle of the bladder and the striated muscle of the sphincter. The purpose of antimuscarinic drugs is to relax the isolated detrusor muscle. Anticholinergic medication acts on nerve terminals that block contractility of the normal bladder. These agents decrease parasympathetic input to the bladder and can effect the bladder capacity by reducing contractility. Either oxybutynin or tolterodine are prescribed to manage uninhibited bladder spasms and symptoms of urgency and frequency (14,36,37). Common side effects of anticholinergic medications include dry mouth, blurred vision, constipation, tachycardia, transient facial flushing, drowsiness, and headache. Anticholinergic medications are administered orally or intravesically to minimize the side effects associated with oral treatment. Intravesical installation requires catheterization, making this a difficult route unless clean intermittent catheterization is already in effect. Dropout rates from intravesical instillation of oxybutynin are reported to be as high as 50% in children with detrusor hyperreflexia (36). Anticholinergic medication assists with biofeedback training in children who have low-capacity bladders or those who have uninhibited bladder contractions (38).

α -Adrenergic antagonist medications may also be prescribed for children with voiding dysfunction. α -Antagonists (Doxazosin or Terazosin) initiate smooth muscle relaxation of the bladder neck and proximal urethra that results in improved bladder emptying and decreased postvoid residuals at lower detrusor pressures. α -Blockers also have an intrinsic influence at the bladder level that produces a change in bladder receptor activity. This effect results in decreased uninhibited bladder contractions and external sphincter activity. The nonselective nature of the medication may result in adverse reactions, including dizziness, asthenia, headache, rhinitis, and hypotension (39).

Tricyclic antidepressants (imipramine) are used to facilitate urine storage by decreasing detrusor contractility and increasing outlet resistance. Imipramine used to treat monosymptomatic nocturnal enuresis. The mechanism of action is unclear but it may exert a local anesthetic

action on the bladder. Other theories include that tricyclic antidepressants act as a stimulant, lightening the level of sleep and making arousal to a full bladder possible. Side effects include fatigue, tremor, skin rashes, mood alteration, sedation, nausea, vomiting, headache, lethargy, irritability, and possible cardiotoxicity. Imipramine should be discontinued slowly to prevent side effects. Advise families to store this drug safely as it may cause accidental poisoning if swallowed by younger siblings (14). The usual dosage range is 1 to 1.5 mg/kg, which may be continued for 3 to 6 mo.

Behavioral Management

Behavioral therapy approaches have commonly been used in conjunction with medical management to treat voiding dysfunction for at least 20 years (40). Children learn a variety of behavioral skills, such as the ability to discriminate body messages, hygiene skills, and eating habit modification. Behavioral therapy generally includes reward systems that reinforce desired behavior.

DIET AND FLUIDS

Noninvasive treatments for urinary incontinence include diet modifications. Reductions in bladder irritants are one of the most commonly recommended treatments. Bladder irritants such as caffeine, chocolate, citrus drinks, and red and blue food coloring have been associated with increased bladder irritability. In addition, health care providers commonly recommend increased water intake as well as adequate fiber consumption.

TOILETING DIARIES

It is extremely useful for patients to keep records of their voiding habits. Toileting diaries allow the health care practitioner and the client to discuss relationships between voiding habits and voiding dysfunction symptoms. Data from diaries can be tabulated to allow objective evaluation of treatment outcome. In addition, retrospective recall of voiding patterns is often problematic and inaccurate.

TIMED VOIDING

Patients are also taught the importance of voiding regularly. This involves teaching families how to establish a voiding schedule with intervals of 2 to 3 hrs (minimum of six voids per day). The children are also instructed about the appropriate position that allows them to achieve optimal relaxation of the pelvic floor while using the toilet. Children with voiding dysfunction often benefit from using a stool to support their feet and enable their pelvic region to relax (41). In addition, deep

breathing and relaxation techniques are taught to children who continue to have difficulty achieving relaxation using positioning strategies.

Often, children with PVRs are taught to double void to completely empty their bladder. Strategies for double voiding include returning to the toilet within 5 min of voiding to empty the bladder or reading several pages of a book and then attempting to void again (42).

SCHOOL INVOLVEMENT

It is critical for treatment of voiding dysfunction to occur at school as well as at home. Patients often report that teachers do not allow free access to the bathroom or that scheduled bathroom breaks do not allow adequate time for implementation of relaxation routines. In addition, many patients report that teachers do not seem to understand that voiding dysfunction is a medical condition that requires timed voiding and adequate fluid intake during school hours. For some patients, it is necessary to contact a school administrator to arrange for accommodations that will allow for appropriate management during daytime hours.

Pelvic Muscle Retraining

In the treatment of voiding dysfunction, the lower pelvic muscles are retrained both to enhance urethral resistance by increasing the strength and endurance of the periurethral muscles and to promote a coordinated response between the bladder detrusor muscle and the voluntary urinary sphincter. Pelvic muscle retraining is hypothesized to improve cortical inhibition over lower urinary tract functioning. Pelvic muscle retraining can occur with or without the use of biofeedback instrumentation.

KEGEL EXERCISES

The retraining program entails teaching children Kegel exercises and short bursts of pelvic floor contractions known as quick flicks that promote contraction and relaxation of the pelvic muscles. Parents and children are taught to use verbal cues to perform pelvic muscle exercises correctly. The children are asked to perform pelvic muscle exercises twice daily starting with three to five repetitions. Often it is difficult for children to isolate contracting the pelvic floor separately from the hip and abdominal muscles. In addition to regular practice of Kegel exercises, quick flicks are used as a means of interrupting a bladder spasm for those children who have significant urinary urgency.

BIOFEEDBACK

Biofeedback is a form of behavior therapy that provides visual and/or auditory feedback about the physiologic functioning of targeted

muscle groups. Children may have difficulty understanding verbal explanations regarding the importance of relaxing and contracting the muscles in their pelvic region, thus biofeedback serves as tool to make the recommendations more concrete. The efficacy of biofeedback training as an effective and noninvasive treatment in the management of sensory urgency, urge incontinence, enuresis caused by detrusor overactivity, and voiding dysfunction caused by detrusor-sphincter dysynergia has been well documented (35,43).

The objective of biofeedback is to learn or relearn how to impact involuntary functions. In-office training opportunities serve as a monitor of progress toward functional goals. Biofeedback therapy is most frequently performed with a two-channel analog chart recorder that allows for simultaneous monitoring of EMG patterns (44). The literature also contains some examples of using uroflow devices as biofeedback instruments (45–47). Whereas internal probes are frequently used in incontinent adults, surface EMG leads are most often used with children. EMG sensors are placed on the perineum and abdominal wall so that electrical signals used to identify pelvic muscle performance can be read. Some practitioners use biofeedback protocols that incorporate games during training, and others may use computer games as a reward at the end of the session.

During biofeedback, the pelvic musculature is evaluated for resting tone as well as for phasic and tonic activity. In addition, abdominal muscles are monitored to ensure isolation of the pelvic muscles. Children are taught how to voluntarily contract and relax the lower pelvic muscles and the bladder sphincter. The aim of the training is to achieve adequate relaxation of the sphincter during micturition and volitional contraction of the external sphincter when needed to manage a bladder contraction in the absence of a readily available toilet.

Yamanishi et al. examined the effect of biofeedback training on incontinence rates in children with sphincter dysynergia (21). They reported a cure rate of 66% for daytime and nighttime incontinence and resolution of detrusor overactivity in 30% of the children managed with biofeedback training. The authors suggested that the high rate of improvement was the result of simultaneously monitoring the abdominal and pelvic muscles. Failures occurred in children who were under the age of 10 yr or who had an IQ less than 60. Similarly, Herndon et al. reviewed their experience with 168 children who were treated with interactive computer games for pelvic muscle dysfunction (48). The majority of patients were treated without medication. Subjective improvement was noted in 87% of the patients. Factors that predicted

failure included small functional bladder capacity (< 60% of predicted) and noncompliance with the treatment program.

Evaluating Outcomes

Recommendations from the International Continence Society for assessing the outcome for treatment of incontinence in children with lower urinary tract dysfunction can be used to determine continence results. They recommend reevaluation after 6 mo to determine the long-term outcome of therapy (15). Sustained improvement involves monitoring the number of wet episodes 6 mo after completing the voiding program. According to the International Continence Society, outcome is divided into three categories. Children with a 90% reduction in daytime wet episodes will be classified as complete cure. Partial success is categorized as a 50% reduction in daytime wet episodes. Children with no improvement in urinary continence are graded as failure.

NOCTURNAL ENURESIS

Nocturnal enuresis is defined as wetting the bed while sleeping beyond the age of expected dryness. Nocturnal enuresis is separated into two categories: primary and secondary. Primary nocturnal enuresis (PNE) affects 5–10% of children over age 5 yr and includes children who have never been dry at night for any length of time. PNE can be unrelated to bladder dysfunction. Secondary nocturnal enuresis is found in children who have been dry for a period of 6 mo (48). The spontaneous resolution rate is approx 15% a year so that less than 1–2% of children will continue to wet the bed at age 15. PNE is a multifactorial problem. Suggested explanations for PNE include the following: delayed functional maturation of the central nervous system that results in inability of the brain to perceive bladder stretch and filling, genetic factors (gene located on chromosome 13), normal sleep cycles but difficulty awakening when various sensory signals are used, and upper airway obstruction alleviated by a tonsillectomy and adenoidectomy (48,49). If both parents have a history of enuresis into adolescence, their child has a 77% chance of PNE; if one parent has a history of enuresis, there is a 44% risk of enuresis; and if neither parent has enuresis, the risk is less than 15%. Three options are available for the management of nocturnal enuresis: benign neglect, alarm systems, and medication.

Alarm Systems

A moisture-sensing device is inserted into the underwear and is activated when the child voids while sleeping. The following advice

should be given to families using a conditioning alarm: (1) emphasize that the treatment plan requires a 3- to 5-mo commitment; (2) encourage them to keep a diary for 1 to 2 wk before starting the program and record the number of episodes during a night, number of wet nights, and amount of wet spot intermittently throughout the program; (3) encourage full participation of the parents; and (4) reward arousal. Families require frequent follow-up, approximately every 3–4 wk, and the child should continue to use the alarm until they have 14 consecutive dry nights. Moffatt recommended overlearning the target behavior by increasing bedtime fluids to a goal of 16 ounces and attempting to achieve 14 consecutive dry nights (48). Houts et al. completed a meta-analysis of studies that included an alarm system as one arm of the study (50). Success rates were reported at 66%, with long-term results of 51% defined as a decline to one night of nocturnal enuresis per month. In a study of long-term outcomes, children managed with an alarm system were more likely to be dry 1 yr after treatment (50). However, these results are not generalizable to all populations of children with PNE because the subjects of this study self-selected to the treatment group.

Desmopressin (DDAVP)

DDAVP is a natural pituitary hormone with antidiuretic hormone activity that has a prolonged and specific antidiuretic function with few side effects. It is useful in the treatment of nocturnal enuresis because of its ability to decrease urine formation by 50% for 8–10 h. There is a reciprocal increase in urine osmolality. It is available as an oral tablet that can be chewed or crushed. It is also available as a nasal spray without affecting the bioavailability of the drug (51). DDAVP is a symptomatic treatment for NE, and there is a high relapse rate after the drug is withdrawn. The drug can be safely used for 12 mo. Higher response rates are reported in children older than 9 yr and those with a history of fewer wet nights. Although it is not curative, DDAVP can be very helpful for special occasions such as sleepovers or camp. It is administered as a nasal spray with a metered dose of 10–20 µg per nostril or orally with a maximum dose of 0.6 µg daily. Families should be instructed to avoid giving the child fluids in the evening after the medication is administered.

SUMMARY

Voiding dysfunction is a common problem that occurs in toilet-trained children who are older than 4 yr. Children have a variety of symptoms, including urgency, frequency, holding behaviors, incontinence, recur-

rent UTIs, and constipation or encopresis. A complete history and physical examination is obtained to rule out anatomic or physiologic abnormalities of the bladder or kidneys. Children with voiding dysfunction can be successfully managed with behavioral, dietary, and pharmacologic therapies. In a select population of children with detrusor-sphincter dysynergia and/or recurrent UTIs, biofeedback may be necessary.

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10 Neurogenic Bladder and Bowel

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INTRODUCTION

Myelodysplasia is a common variant of neural tube defects, occurring in 1:1000 live births in the United States and estimated to affect 300,000 children worldwide. Classification as closed or open depends on the presence of exposed neural tissue or tissue covered by a thin membrane. Approximately 20% of children have associated congenital anomalies. Despite new surgical advances and *in-utero* procedures, children with neural tube defects have a variety of complex and challenging orthopedic, neurosurgical, and urologic problems that require careful assessment and lifelong management to reduce disability and improve quality of life.

ANATOMY AND PHYSIOLOGY OF VOIDING

The urinary bladder has two functions: storage and elimination of urine. Normal storage depends on a high degree of bladder compliance and a competent sphincter mechanism. Normal elimination requires coordination between the bladder and external sphincter.

Voiding is a function of spinal reflexes that are facilitated and inhibited by higher brain centers. Three sets of peripheral nerves are involved: sacral parasympathetic, thoracolumbar sympathetic, and sacral somatic nerves. Afferent nerve fibers from the bladder, urethra, and sphincters enter the thalamus and convey impulses to the parietal cerebral cortex. The sympathetic nerves do not play a role in micturition. Contraction of the detrusor muscle occurs secondary to parasympathetic excitation, causing the bladder to contract. Sensory nerves leave the bladder and enter the spinal column through the pelvic nerves and sacral plexus (sacral parasympathetic, S2–4). The pudendal nerve that originates in the first two sacral segments (sacral somatic nerves) of the spinal column innervates the external sphincter. Sympathetic nerve fibers from the lumbar region (thoracolumbar sympathetic T10–L12) cause the bladder to relax. As the bladder reaches capacity, numerous micturition contractions may occur as a result of the stretch reflex, although these can be inhibited in the normal situation. There is a decrease in urethral pressure that precedes the increase in bladder pressure during normal voiding, suggesting that urethral relaxation is the first step in micturition (1). There is a feedback mechanism such that the initial contraction activates receptors to increase afferent impulses and bladder contractions.

The increase in frequency and intensity of the contractions is sustained for approx 1 min and then the muscle returns to a basal tone. This

cycle will reoccur until the bladder is emptied, with increasing strength and frequency of the contractions.

Abnormal functioning of neurogenic bladders depends on the type and level of neurologic injury but often includes uninhibited contractions, uncoordinated function of the detrusor muscle and the pelvic muscles, poor bladder compliance, inadequate urethral closure, or hyperreflexia (defined as uninhibited bladder contractions in the face of a known neurologic lesion).

SPINAL DYSRAPHISM

Defects in formation of the neural tube occur during the first 3 wk of gestation and cause significant developmental malformations of the brain and spinal cord. These disorders are known as dysraphic defects (2). This is an inclusive term that describes the spectrum of developmental abnormalities that occur in the midline of the back from the skin to the vertebral bodies.

MYELOYDYSPLASIA

Spina bifida (SB) is an example of a dysraphic defect. The three most common types of SB are myelomeningocele (MMC), meningocele, and SB occulta. In MMC, the spinal cord and its protective covering protrude from an opening in the malformed bony spine. A meningocele has a normal spinal cord but protrusion of a meningeal sac filled with spinal fluid. Occulta, a closed defect, is the least severe form of SB. In this condition, one or more vertebrae are malformed and covered by a layer of skin. Examples include lipomeningocele and diastematomyelia. An SB occulta often is accompanied by hemangiomas, nevi, or hairy patches over the skin-covered lesion (3).

Children with MMC often have a central nervous system defect known as Arnold-Chiari type II malformation, in which there is a downward displacement of the cerebellar vermis into the cervical spinal canal. This results in elongation of the brainstem and obliteration of the fourth ventricle. The resulting obstruction contributes to the development of hydrocephalus late in gestation or after postnatal closure of the spinal defect (4). The findings include early fusion of the bones in the posterior fossa.

Insufficient space in the cranial vault for the cerebrum, cerebellum, and brainstem obstructs the flow of cerebrospinal fluid (CSF) and contributes to hydrocephalus (3,5). Clinical symptoms of Arnold-Chiari in infants may include difficulty swallowing, inspiratory stridor, weak or poor cry, and head arching or apnea. If symptoms persist, the child may demonstrate weakness and decreased sensation of the hands and feet. Surgical

management of Arnold-Chiari involves posterior fossa decompression with laminectomies to allow more space for the brainstem structures.

Children with MMC are also at risk for behavioral and emotional problems that may be related to the midline abnormalities of the brain. When compared with controls, children with MMC demonstrate deficits in IQ and have decreased verbal skills and visual perceptual and visuospatial skills. Academic testing usually indicates deficits in mathematics. Bilenber and Lie examined the symptoms of attention deficit hyperactivity disorder in children with MMC and found a high incidence of inattention but few problems with hyperactivity or impulsivity (6). Hommeyer et al. reported similar findings in children with more severe symptoms of MMC such as shunted hydrocephalus (7).

In 18–40% of children with myelodysplasia, there is a risk for latex and ethylene oxide allergies. Possible explanations for the sensitization include exposure from multiple surgical procedures or repeated catheterizations. The allergic response varies from allergic rhinitis, vasodilatation, edema, hives, rash, and wheezing to anaphylaxis. The response occurs when the child's skin comes in contact with latex products, although surgical contact and respiratory exposure have also been known to result in allergic reactions. Potential sources of medical latex exposure include gloves, tape, catheters, latex ports used in intravenous tubing, rubber tourniquets, vial stoppers, wheelchair wheels, Ambu bags, and stethoscopes (8). In a study comparing children with SB with children undergoing multiple surgical procedures, Porri et al. found that children with a history of multiple surgical procedures (> 6) were also at high risk for latex sensitization (9).

The degree of neurologic deficit in MMC is related to the level of the lesion, although level is often not predictive of bladder behavior. Lesions below the second sacral vertebra do not usually involve orthopedic problems. Spinal defects at or above the upper sacral area result in more significant orthopedic, neurologic, and urologic deficits that include neurogenic bowel and bladder. Lesions higher in the cord with preservation of reflex sacral function can result in bladder-sphincter dyscoordination.

In children with detrusor-sphincter dyssynergia, sphincter activity increases during bladder contraction or sustained increases in bladder pressure. The free flow of urine is impeded during a voiding contraction. The risk of upper urinary tract damage varies from approx 16 to 39% of children with SB (10). Renal damage is most often associated with vesicoureteral reflux (VUR), recurrent pyelonephritis, and elevated detrusor pressures, and is most commonly associated with urodynamic findings of high leak point pressure and/or bladder-sphincter dyssynergia.

Prenatal detection of MMC most often occurs through routine screening of alpha-fetoprotein (AFP) levels, which occurs during the first trimester. If elevated levels of AFP are detected, amniocentesis and fetal ultrasonography are recommended. Prenatal diagnosis has made it possible to counsel parents prenatally. If completion of the pregnancy is elected, families may consider several options in the management of the fetus with MMC. These include fetal surgery and planning for delivery at a tertiary care center with or without cesarean section delivery as well as the prospect of many postnatal surgeries.

Fetal surgery has generated a significant degree of controversy in the management of nonlethal conditions such as MMC and the impact on outcomes. In a retrospective study, Holmes et al. examined urodynamic findings in newborns who underwent fetal surgery (11). The findings indicated that infants with SB who underwent fetal closure of their spinal defect undergo similar urodynamic and anatomic changes to those of children managed in a standard manner in the postnatal period. However, the infants have the additional burden of potential effects of premature delivery. A randomized clinical trial is recommended to evaluate the long-term urologic outcome in children with SB.

Animal studies in fetal sheep have shown that early closure of the spinal cord can decrease cord dysplasia and preserve function because the cord is not exposed to amniotic fluid and trauma. It has also been suggested that early closure may prevent the development of Arnold-Chiari malformations because normal cerebral spinal fluid dynamics are restored with adequate blood flow. Olutoye and Adzick have suggested that *in utero* repair of the child with MMC before 24 wk of gestation prevents the neural damage caused by the exposed spinal cord and allows for maximal regenerative potential of the unmyelinated spinal cord during the third trimester.

The recommendation that women take a folic acid supplement before conception and during the first trimester of pregnancy is a key advance in the management of MMC.

A diet high in enriched grains (supplemented with 140 µg of folic acid per 100 g of grain) or supplementation with 400 µg of folic acid daily is recommended for pregnant women.

TETHERED CORD SYNDROME

Tethered cord syndrome (TCS) can occur with a variety of dysraphic conditions. TCS occurs when the spinal cord is abnormally caught between immovable structures such as scar tissue or lipomatous material at the caudal or cranial end of the cord. Consequently, the normally

relaxed spinal cord is pulled and stretched as the child bends, moves, and grows. The resulting unnatural forces damage the blood vessels, nerve cells, and nerve fibers, or alternatively, result in ischemic changes to the cord. Cutaneous findings of spinal dysraphism and TCS as part of an occult SB defect (SB occulta) may include lumbosacral cutaneous hemangiomas, hypertichosis dermal sinus, subcutaneous lipoma, and skin appendages. Approximately 75% of patients with TCS have neurologic changes such as radicular pain, weakness, asymmetric hyporeflexia, spasticity, sensory changes, and bowel/bladder dysfunction. The lower motor neuron symptoms may be caused by compression of the cord compared with upper motor neuron symptoms that are related to ischemic damage caused by the tethered cord. Orthopedic changes associated with TCS include foot deformities, limb length discrepancies, atrophy of the legs, gait disturbances, limb pain, and scoliosis. Bone abnormalities found in patients with TCS include bifid vertebrae, laminar defects, hemivertebrae, sacral aplasia, sacral agenesis, and multiple segmentation errors (13). New onset of urinary or bowel incontinence or changes in urodynamics with or without urinary tract infection (UTI) may be urologic indications of TCS. TCS has been suggested as a cause of neurogenic hyperreflexia of the bladder despite a normally positioned conus medullaris, normal terminal filum, and SB occult or orthopedic and vertebral abnormalities (13) based on improvement in urinary symptoms after division of the filum.

The most common cause of progressive neurologic, urologic, and orthopedic deterioration is congenital tethering of a lipomeningocele (14). Timing of surgical intervention remains controversial if the patient is asymptomatic, however, most authors recommend early untethering to prevent neurologic deterioration. Frequent assessment of neurologic and urologic function is required throughout the child's life to assess for recurrence of the tethered cord. A variety of modalities are used, including clinical assessment, radiologic examination, and urodynamic testing.

Torre et al. compared results of electrophysiologic examination with electromyographic (EMG) detection of the perineal muscle activity and sacral reflexes with urodynamic results and clinical findings in children with spinal dysraphism. The electrophysiologic examination was highly sensitive in predicting urodynamic impairment in children with bladder-sphincter dyssynergia (100%) or bladder dysmotility (86%) (15). The authors recommended electrophysiologic examination for children with minimal urologic symptoms of TCS and said that invasive urodynamic studies should be preserved for children with progressive symptoms of neurogenic bladders.

TCS can be primary (resulting from a form of SB occulta) or secondary to previous closure of a dysraphic defect. Tarcan et al. examined the urologic outcome of newborns with SB and initially normal urodynamic studies (16). The findings indicated a 32% risk of urologic deterioration related to spinal cord tethering by age 6 yr. Children with myelodysplasia are at risk for tethered cord resulting from postoperative adhesions or infection after the initial closure of the defect. Tethered cord may occur within weeks of closure of the defect or several years later until after pubertal growth is complete (secondary). Clinical manifestations are the result of ischemic changes or tension on the cord and often include a subtle change in bowel or bladder function. The usual treatment is surgical release of the tethered cord, but this does not always reverse the urologic problems, and it may worsen the symptoms or create new problems. Generally, the shorter the duration of urologic symptoms (infection, urgency, and incontinence), the more likely the child will stabilize or improve in the long-term.

SACRAL AGENESIS AND CAUDAL REGRESSION SYNDROME

Sacral agenesis is described as congenital absence of the whole or of part of the sacral vertebrae S2–S5. When associated with anorectal malformations (anal atresia, rectovaginal fistula), a presacral mass and hemisacrum, the triad of anomalies is known as Currarino syndrome and is localized on chromosome 7q36. Caudal regression is characterized by premature termination of the vertebral column (17,18). Embryologically, the vertebral column and genitourinary systems are formed simultaneously from mesodermal tissue before 8 wk of gestation. Approximately 15 to 25% of mothers of these children have insulin-dependent diabetes and have a 250 times increased risk of caudal regression than those without diabetes. There is variability in expression of the disease, with a high incidence of renal/urinary tract problems.

Frequently, children with involvement of the coccyx alone and/or the last two sacral segments are asymptomatic. Sacral agenesis generally represents a fairly fixed neurologic deficit, as opposed to SB. Further evaluation is required if neurologic deterioration is noted (19,20).

UROLOGIC EVALUATION

A baseline renal and bladder ultrasound is recommended shortly after birth. Ultrasound should be repeated every 3 mo during the first year of

life, twice in the second year of life, and then on a yearly basis, but may be repeated sooner if recurrent UTI, hydronephrosis, or incontinence develops. This test serves as a baseline as well as providing a regular indicator of the health of the upper tracts and state of the bladder. Less frequent ultrasonography is reasonable if urodynamic findings, as discussed below, suggest a low risk for renal deterioration.

The purpose of urodynamic testing in the newborn is to evaluate bladder pressures and identify bladders that put the upper tracts at risk for deterioration. Later studies are used to guide clinical management of urinary incontinence. The majority of children with myelodysplasia have urodynamic abnormalities that require close urologic evaluation and follow-up. Approximately 6.5 to 12% of newborns will have abnormal urodynamic parameters (16,21,22).

Although some advocate expectant management with serial renal ultrasounds, most children undergo initial urodynamic studies within the first 1 to 2 mo of life. Urodynamic studies include a neurologic evaluation of the perineal region, cystometrography, and external EMG of the pelvic diaphragm. Urodynamic findings in children with MMC include uninhibited bladder contractions, bladder areflexia, decreased compliance, and detrusor-sphincter dyssynergia. Fluorourodynamics allow simultaneous voiding cystourethrography, which otherwise should be performed to rule out VUR. Recently, urodynamic studies of children undergoing neural tube repair at approx 27 wk of gestation were compared with those of children undergoing repair in the neonatal period. No difference was found in the incidence of uninhibited bladder contractions, hypotonia, or bladder compliance (23). It is unclear whether early intervention will affect long-term continence. Cystometrography is performed with a 7-Fr dual lumen catheter inserted transurethraally into the bladder.

Normal saline is infused into the bladder at a rate approximating 10% of expected bladder volume per minute. Total intravesical and detrusor pressures are differentiated by subtracting abdominal pressure obtained by means of a rectal balloon. Detrusor pressure is monitored during the filling phase, with simultaneous documentation of EMG activity of the external urethral sphincter. Parameters assessed during urodynamics include bladder capacity, compliance, detrusor contractility, and maximum bladder capacity with leak point pressure. Evidence of bladder-sphincter dyssynergia includes increased EMG activity just preceding a bladder contraction or gradually increasing EMG activity with progressive increase in bladder filling and pressure.

The functional, or safe, bladder capacity is defined as the volume of liquid held at pressures below 40 cm H₂O. Likewise, a dangerous leak

point pressure for children who empty spontaneously is greater than 40 cm H₂O. This is based on classic studies by McGuire, who showed that upper tract deterioration was unlikely if pressures were kept below this level most of the time (24).

The goal of urologic care is to prevent urinary tract deterioration and to promote continence at the appropriate age. Intervention may include a combination of anticholinergic medication and clean intermittent catheterization (CIC), as well as surgical procedures to increase or decrease bladder outlet resistance and increase bladder compliance. The mechanisms of incontinence are diverse and include overflow evacuation caused by detrusor instability and a nonrelaxing sphincter, limited storage capacity caused by hyperreflexia and poor compliance, and low urethral resistance from sphincter denervation (25)

MANAGEMENT OF URINARY INCONTINENCE AND HIGH-PRESSURE BLADDER

Clean Intermittent Catheterization

CIC is a safe and effective long-term method to manage neurogenic bladder in children. The purpose of CIC is to allow complete bladder emptying at low pressures. A variety of catheters and methods are available for the procedure. Water-soluble lubricant or anesthetic jelly can be applied to the catheter or urethra for easier insertion. Many patients with limited mobility of the upper extremities prefer a hydrophilic catheter that is self-lubricating and is activated in sterile or tap water (26). The meatus is cleaned with a towlette or soap and water. Gloves are not required if the child or caregiver uses good hand-washing technique before catheterization. The catheter is washed with soap and water and air-dried. Studies show that sterilization or cleaning catheters by microwaving the catheter on high for 2 min is not more effective in decreasing symptomatic infections (27). Generally, the catheter can be re-used for approx 3–4 wk until it becomes cracked and dry. Children usually catheterize every 3–4 h, but this is based on safe bladder capacity and the goals of therapy. Children younger than 5 yr depend on their parents or caregiver for assistance with catheterization. Independence with catheterization is also influenced by the position of the child. The easiest position for catheterization is on a flat surface bed or table or in a position where the child is reclining. More difficult positions include a wheelchair or toilet (28).

Stagnated urine that results from incontinence, urinary retention, and bladder hypertonia is a frequent finding in children with a neurogenic bladder. The result is recurrent UTI and potential renal damage. Differ-

entiating UTI from colonization in an asymptomatic patient with a neurogenic bladder is difficult. Children with positive urine from multiple organisms or a single organism but no symptoms are not actively treated with antimicrobial therapy. The following symptoms may or may not be present: temperature higher than 38°C, pyuri (>10 white blood cell count/heparin-precipitable fraction), bacteriuria greater than 10⁵ colony-forming units, unusually cloudy urine, abdominal pain, emesis, malodorous urine, diarrhea, or more frequent incontinence. Szucs et al. examined the urine in asymptomatic children with SB managed with CIC (29). The findings suggest that asymptomatic patients with SB who have bacteriuria and elevated Interleukin-8 levels have a true infection rather than colonization.

Pharmacologic Intervention

Pharmacologic treatment is initiated to reduce upper tract risk or to enhance urinary continence. Inadequate bladder storage capacity is improved by lowering the detrusor tone or reducing uninhibited bladder contractions with anticholinergic medications such as oxybutynin chloride, tolterodine, or tricyclic antidepressants (imipramine). Anticholinergic agents inhibit the binding of acetylcholine to the cholinergic receptors and inhibit bladder smooth muscle contraction, thereby increasing total bladder volume. Anticholinergic medications are usually administered orally. Some are available in immediate or prolonged release forms. Side effects of anticholinergic medications include dry mouth, constipation, drowsiness, and cognitive dysfunction.

Poor patient adherence because of medication-related adverse events often results in dose reduction or discontinuation of the medication. Intravesical administration of oxybutynin at a dose of 0.2 mg/kg twice a day is an alternative to manage the dysfunctional bladder in children who are using CIC. Several important neurologic side effects have been noted with intravesical administration of oxybutynin, including hallucinations, drowsiness, and cognitive impairment. Reabsorption of intravesical oxybutynin is slower compared with orally administered medication, resulting in more frequent central nervous system effects. These children require careful monitoring to ensure their safety (30). Sympathomimetic agents such as ephedrine sulfate that stimulate alpha-receptors in the bladder neck may be used when there is inadequate urethral resistance that causes impaired storage, although tachyphylaxis commonly occurs (25).

Surgical Management

Surgery for neurogenic bladder can be done to promote safe bladder pressures, urinary continence, or both. Goals related to urinary

continence include creating a high-volume, low-pressure bladder and obtaining adequate outlet resistance. Preoperative evaluation includes urodynamic testing, laboratory studies, and radiographic studies to assess for bladder compliance, bladder outlet resistance, existing bladder capacity, electrolyte abnormalities, renal impairment, and anatomic abnormalities of the upper and lower urinary tract (31–33). The family and child should be assessed for the ability to comply with CIC if they will be required to continue this procedure in the postoperative period.

Reducing Leak Point Pressure

In the infant with high intravesical pressure and upper tract changes, initial management is anticholinergic medication and intermittent catheterization. When this fails, surgical approaches may be considered. Although bladder pressures can be decreased through the use of bladder augmentation, most would consider this treatment to be overly aggressive for infants and young children. The focus is generally on decreasing the leak point pressure, which can be accomplished by creating an alternate exit route for urine (vesicostomy) or by decreasing the resistance at the level of the sphincters (urethral dilation).

Vesicostomy

This procedure involves exteriorizing a portion of the native bladder to the skin, forming a direct urinary conduit. A retrospective study identified 23 patients with myelodysplasia who had undergone cutaneous vesicostomies for various reasons: hydronephrosis, recurrent UTI, developmental delay, VUR, and failure to perform intermittent catheterization. Hydronephrosis resolved in 100% of patients. Although surgical reconstruction of the urinary tract is the preferred method for treating elevated intravesical bladder pressures and preserving renal function after failure of medical therapy, temporary or even permanent vesicostomy diversion is a successful technique to prevent recurrent UTIs and preserve renal function in selected patients (34).

Urethral Dilation

The use of external urethral sphincter dilation for the management of patients with myelodysplasia who have elevated leak point pressures and and/or poor bladder compliance has been in practice for more than 30 yr. A recent retrospective review of 25 patients who underwent this procedure demonstrated that this method improved urodynamic parameters and prevented upper urinary tract damage in a select group of patients (25). The authors found that patients with significantly abnor-

mal urodynamic parameters and uninhibited detrusor contractions were less likely to respond to this treatment.

Increasing Bladder Compliance

Neurogenic incontinence is often caused, at least in part, by poor bladder compliance or intractable hyperreflexia. Methods to increase compliance and capacity or to decrease contractions include electrostimulation and bladder augmentation.

ELECTROSTIMULATION

Electrostimulation has been used to modulate the characteristics of the neurogenic bladder. In children with SB, this has consisted of intravesical electrostimulation of the bladder itself (36).

For those with intractable neurogenic or nonneurogenic urge incontinence, sacral root stimulation with implantable electrodes has been used. Contraindications for bladder stimulation therapy include previous augmentation, grade 5 VUR, complete spinal cord lesions, or persistent severe infection.

Complications that may arise with surgically inserted electrostimulation units include electrode migration, superficial wound dehiscence, and infection (37). The benefits of electrostimulation include improvement in symptoms of urinary urgency, functional bladder capacity, a decrease in leakage episodes during stimulation, and avoidance of surgical bladder augmentation. These benefits have not been noted in all series, and bladder electrostimulation is currently practiced at only a few centers. Using implantable sacral root electrodes, Chartier-Kastler et al. reported symptomatic improvement in nine patients with neurogenic bladder who had increased bladder capacity and volume to first uninhibited contraction on urodynamic studies (38).

BLADDER AUGMENTATION

Autoaugmentation. Snow and Cartwright described an alternative approach to gastrointestinal (GI) augmentation that involved excision and blunt dissection of the detrusor muscle from the underlying mucosa (39). A large bladder diverticulum is created that improves compliance and decreases intravesical pressures (40). In this approach, the entire procedure can be performed extraperitoneally. Eliminating the use of intestinal segments avoids the risk of bowel obstruction, metabolic complications, and mucus production, and decreases the risk of malignancy, stone formation, and UTI. This procedure does not increase bladder capacity to the extent of an intestinal augmentation, and therefore the ideal patient should have a reasonable bladder capacity with a poorly compliant bladder. Pre-

liminary long-term results in a small series of patients demonstrated poor outcomes in 7 of 11 patients, who required a second procedure with enterocystoplasty (41). Careful evaluation of the appropriate candidate is necessary to ensure success with auto-augmentation.

Ureterocystoplasty. The procedure involves taking a massively dilated ureter, incising it vertically, and attaching it to the bladder to form a spherical container (42). This results in increased bladder capacity and improved continence (43). Unfortunately, this technique is limited to a select group of patients who have a large hydroureter and a nonfunctioning kidney. Given the early institution of anticholinergics and CIC in most myelodysplastic patients, this scenario is not often encountered.

The benefits of using native urothelium in both autoaugmentation and ureterocystoplasty include lack of mucus production that minimizes the risk of forming stones and developing infections, decreased rates of malignant transformation, and reduced metabolic complications compared with GI augmentations (43).

Enterocystoplasty. The most common form of bladder augmentation uses a segment of the GI tract as a patch on the bladder. Ileum, sigmoid, cecum, and stomach have all been used. Jejunum is avoided because of the high likelihood of metabolic consequences (44). As part of the procedure, the native bladder must be bivalved aggressively or incised in a stellate pattern to avoid creating a large bladder diverticulum following placement of the intestinal segment on the bladder (45). In general, a 15- to 25-cm segment of ileum or colon is isolated, detubularized, and reconfigured into a U, S, or W shape and sewn onto the bivalved native bladder, creating a spherical reservoir (46–48).

Ileocystoplasty. The most common type of augmentation performed is ileocystoplasty. This procedure involves resection of ileum at least 10 to 15 cm proximal to the ileocecal valve to preserve the function of the distal terminal ileum (bile salt reabsorption and production of vitamin B12). As described previously, the segment of ileum is detubularized, reconfigured into a U, S, or W shape, and sewn to the bivalved bladder, forming a spherically shaped reservoir. One disadvantage of this approach is that the longer distance from the ileal segment to the bladder may result in tension on the bladder anastomosis (33).

Sigmoid Cystoplasty. The approach and technical aspects of this procedure are similar to those for ileocystoplasty. The sigmoid colon is often large, redundant, and in close approximation to the bladder in children with MMC, making it an excellent segment for augmentation. The position of the sigmoid facilitates the anastomosis to the bladder. However, higher rates of mucus production and higher enteric contraction rates have been reported (33).

Gastrocystoplasty. In patients with renal insufficiency, short gut syndrome, or irradiated bowel, the use of the stomach is the preferred alternative for augmentation.

A wedge-shaped piece of stomach is isolated and its blood supply is preserved; it is mobilized through the transverse colon mesentery and sewn to the bladder (49).

Significant metabolic abnormalities may be associated with gastrocystoplasty, including hyperchloremia and metabolic alkalosis (50). Another potential consequence is the hematuria-dysuria syndrome, which can be significant enough to require removal of the gastric segment (51).

Autoaugmentation Combined with Demucosalized Bowel or Stomach. GI cystoplasty has potential complications and therefore a procedure was developed that uses the advantages of autoaugmentation and GI segments. Seromuscular colocolocystoplasty lined with urothelium involves excising the detrusor muscle from the underlying urothelium and covering it with a demucosalized segment of bowel (52). Early results demonstrated that this technique could be a reasonable alternative in a select group of patients (53). Postoperatively, a 2.4-fold increase in bladder capacity was seen as well as a significant decrease in bladder end-filling pressures. No significant complications were reported, and 81% of the patients were continent. The use of demucosalized stomach was also studied by several groups, with less favorable outcomes (54,55). On long-term follow-up, some reports have shown continent rates of less than 50%, with 33% requiring an additional augmentation with an intestinal segment (56).

COMPLICATIONS OF BLADDER AUGMENTATION

Surgical complications of bladder augmentation might include bowel obstruction, bladder perforation, urinary leakage, and continued urinary incontinence requiring further procedures. Bowel obstruction either in the immediate postoperative period from poor technique or in the long-term from adhesion carries a significant risk of up to 10% in a large series (57). Other side effects of enterocystoplasty might include stone formation, mucus production, metabolic derangements, malabsorption, and bladder tumors.

When intestinal segments are interposed into the urinary tract, metabolic and electrolyte disturbances can occur. The type and severity of abnormalities depend on the type of segment used, the amount of surface area in contact with urine, and the renal function of the patient. The use of ileum or colon usually produces a hypokalemic, hyperchloremic metabolic acidosis (44).

To compensate for the increased acid load, the body uses bone buffers, which can lead to bone demineralization. If a significant part of the distal ileum is used, a vitamin B12 deficiency can occur because it is absorbed into the distal ileum (58). Stomach in the urinary tract usually produces a hypokalemic, hypochloremic metabolic alkalosis. In this situation, the stomach secretes acid and potassium is lost in the gastric secretions (59).

Intestinal segments continue their physiologic roles when placed into the urinary tract. As a result, electrolytes are absorbed through active and passive transport mechanisms and mucus is secreted. The sigmoid produces the most mucus followed by ileum and then stomach. Patients who empty their bladder through catheterization may have difficulty completely emptying their bladders. Irrigation of the bladder is recommended at least three times daily in the immediate postoperative period and once daily indefinitely. Mucus can also act as a nidus for stone formation (33).

The most severe complication that occurs following enterocystoplasty is perforation. This is a potentially life-threatening catastrophe if not diagnosed and treated promptly (60). One potential explanation is that chronic overdilation of the augmented bladder resulting from poor adherence to a strict catheterization schedule causes ischemia of the bowel or bladder wall and increases the risk of perforation (61,62). Other explanations suggest that detrusor hyperreflexia can generate high intravesical pressures, leading to ischemic changes (63). Traumatic catheterization has also been a proposed mechanism because the vast majority occurs in those who self-catheterize to empty their bladders. The signs and symptoms include abdominal distension, abdominal pain, fever, nausea, and emesis. Most children with myelodysplasia have impaired sensation, and therefore one's index of suspicion must be high. A computed tomography cystogram is the best test to evaluate these patients for bladder perforation because a plain cystogram has an unacceptable false-negative rate (64).

A rare complication is the formation of a tumor in an augmented bladder. The following tumors have been identified: adenocarcinomas, transitional cell carcinomas, signet ring, cell carcinoma, oat cell carcinoma, and sarcoma (65,66). However, it is unclear whether enterocystoplasty truly increases the risk of tumor formation.

Development of bladder calculi has been reported as the most common complication of enterocystoplasty (67). Stones are a difficult management problem because injury to the bowel and bladder can occur with endoscopic lithotripsy.

Larger stones have generally been removed by an open operation, but more recently, a percutaneous technique has been shown to be as effective as open surgery, with the potential for outpatient management (68). The cause appears to be multifactorial, with persistent bacteriuria, mucus production, and urinary stasis playing roles. Patients with continent stomas tend to have a higher rate of stones, probably as the result of inadequate emptying with catheterization.

Chronic bacteriuria is a common finding after an intestinal augmentation. There is no statistically significant difference in the rate of UTIs among the various segments used (69).

SURGICAL THERAPY FOR BLADDER OUTLET INCOMPETENCE

In addition to problems with bladder storage, incontinence in children with MMC may occur as the result of an inadequate sphincteric mechanism. Several procedures have been developed to manage poor outlet resistance. Commonly performed procedures include the Young-Dees-Leadbetter, Kropp with or without modifications, and the Pippi Salle. Alternatives to bladder neck reconstruction include injectable bulking agents, genitourinary prostheses, and pubovaginal slings.

Young-Dees-Leadbetter

In this procedure, a full thickness, rectangular area of posterior bladder wall from the trigone to the proximal urethra is isolated. This strip of bladder wall is tabularized over a catheter, creating a neourethra (70–72). This technique has been used extensively in children with the exstrophy/epispadias complex, but its success has been questioned for those with SB (73). It has been suggested that failure of this procedure is related to congenital sphincter laxity found in patients with MMC. However, more recently Donnahoo et al. reported reasonable continence rates using the Young-Dees-Leadbetter technique in patients with SB (74). The majority of patients (68%) were dry after just one operation, and nearly all of the remainder of the patients (79%) were dry after one or two additional procedures. Nearly all patients required a bladder augmentation (74).

Kropp Procedure

Through an anterior cystotomy, a rectangular area of anterior bladder wall is tubularized over a urethral catheter with the proximal portion of the tube based at the bladder neck. The tube is then placed beneath a midline submucosal tunnel in the area of the trigone to create a flap-valve.

This technique has demonstrated continence success rates of 77–91% in several series (75–77). Difficult catheterization is the most frequently reported complication, with rates ranging from 28 to 45% (77,78). To achieve adequate urethral lengthening, the ureters must be reimplanted in a cephalad position (79). Modifications of the Kropp procedure have yielded similar continence rates. In these procedures, the anterior bladder wall flap is tabularized but not tunneled beneath the submucosa. Instead a groove is created and the tube is placed onto it (75,76).

Pippi-Salle

This procedure uses the anterior bladder wall flap, as described for the Kropp procedure, but instead of rolling it into a tube and creating a submucosal tunnel, it is placed onto a rectangular piece of midline posterior bladder mucosa and sewn in an onlay fashion (69,80,81). This technique has yielded slightly lower success rates (61–69%) than the Kropp procedure, but there are fewer reported cases of difficulty with catheterization. The most common complication of the Salle procedure has been the development of urethrovesical fistulas, followed in descending order by VUR and bladder calculi (82).

INJECTABLE AGENTS

Bulking agents are injected around the bladder neck and urethra to increase bladder outlet resistance in children with myelodysplasia. Different agents are used with varying results. These include Teflon, collagen, and more recently, dextranomer/hyaluronic acid polymer (83,84). Initially, Teflon was used but recently its use was discontinued related to distal migration of particles and formation of granulomas at distant sites (85). Following its initial success in women with intrinsic sphincter deficiency, collagen use was attempted in children. Early reports were promising, with success rates of 76% (86). However, recent series have demonstrated unsatisfactory continence rates (83,84,87).

Repeated injections are often required approximately every 3 mo. Although a minimally morbid procedure, with few if any complications, endoscopic injections have a limited role in treating incontinence from an incompetent bladder outlet.

ARTIFICIAL URETHRAL SPHINCTER

The artificial urethral sphincter (AUS) is a device composed of an inflatable cuff, balloon reservoir, and pump mechanism for the treatment of urinary incontinence. The cuff is placed around the bladder neck in children. The pump is inserted into the scrotum in males and into the

labia majorum in females. The reservoir is positioned in the space of Retzius, an extraperitoneal location. The AUS is recommended for myelodysplastic children with outlet incompetence and a large capacity, highly compliant bladder, who void spontaneously. It is also used effectively in children who undergo intermittent catheterization.

The AUS has been shown to be effective when used concomitantly or after an enterocystoplasty (88). Approximately 10 to 20% of patients have increased detrusor activity after AUS placement (89). The majority can be managed with anticholinergic medication and intermittent catheterization, but those who fail medical therapy will need a bladder augmentation. Complications include mechanical failure, decreased bladder compliance, cuff erosion, and infection. Studies have demonstrated the durability and overall effectiveness of the AUS in long-term follow-up (90–94).

FASCIAL SLINGS

Fascial slings are an alternative method to manage urinary incontinence in MMC. This procedure involves taking a rectangular piece of autologous rectus fascia or allograft material and suspending the bladder neck. The ends of the graft are tied together over the rectus muscle. This results in elevation and compression of the proximal urethra and bladder neck (95,96). The majority of published series demonstrate a continence rate of between 40 and 100% (97–99) and the reasonable expectation for success is approx 50%. Variations include rectus fascial wraps, in which the rectus graft is tied circumferentially around the bladder neck, providing constant compression (100). Potential complications include difficulty with intermittent catheterization and urethral erosion (101).

ALTERNATIVE CONTINENCE CHANNELS

Bladder neck reconstructive procedures achieve dryness in only 60 to 70% of cases. Therefore, secondary procedures such as closure of the bladder neck or division of the bladder neck are used to achieve continence. Dividing the bladder from the urethra requires formation of a continent urinary stoma that can be accessed by the patient for self-catheterization. The disadvantage of this aggressive procedure is that bladder perforation can occur if catheterization is not performed on a regular schedule. Despite adherence to sound technique, including interposing omentum between the bladder and urethra, a fistula may occur on the urethra (33).

The Mitrofanoff procedure (appendicovesicostomy) is an important adjunct for cases in which the bladder neck requires division or closure and/or when access to the urethra is difficult, as in the patients who are in wheelchairs. This technique is based on the flap valve mechanism, in which pressure from the bladder is transmitted to a conduit tube (preferably the appendix or segment of ileum) tunneled submucosally into the bladder, compressing its lumen (*102*). A variety of options are available to create the catheterizable channel, including the appendix, ureter, stomach, tapered ileum, and bladder flap. The appendix should be preserved in patients with fecal incontinence for future use to create an antegrade colonic enema stoma. The Mitrofanoff channel usually exits through the umbilicus, but a stoma can be created anywhere on the abdominal wall. Outlet resistance is achieved by bladder neck closure, division of the bladder neck, or bladder neck reconstruction. Tekant et al. demonstrated a continence rate of 86% in a series of 46 patients undergoing appendicovesicostomy or the Monti procedure (*103*). The complication rate was 19.5%, but these were easily manageable problems such as strictures at the skin level and mucocoele formation in one case. In another series, the most frequent complications reported were stomal stenosis and stomal leakage (*104*). Umbilical stomas can be completely concealed, and when a posterior umbilical flap is used, the stomal stenosis rate is minimized (*105*).

NEUROGENIC BOWEL

Fecal incontinence is a sequela of neurogenic bowel and affects the quality of life and social outcomes for children and adolescents with SB. A variety of methods are recommended to evacuate the bowel, including voluntary bowel movement, manual evacuation, stool softeners, suppositories, or retrograde irrigation (*106*). Patients with MMC and those with spinal cord injury who lack sensation are unable to consciously initiate reflex defecation. If the lesion is above the level of the conus, the rectocolic reflex may be used to assist the patient to defecate. Digital-rectal stimulation is used to facilitate defecation by inserting a gloved finger into the rectum and applying gentle pressure in the direction of the sacrum. This relaxes the external sphincter and pelvic muscles, initiates peristaltic waves, and allows passage of stool. In patients with lesions below the level of the conus, sphincter tone is lost, eliminating reflex defecation. The bowel must be emptied by other means to prevent fecal incontinence.

Digital rectal stimulation will produce local peristalsis, but disimpaction is required to empty the bowel (*107,108*). The treatment regimen

in children involves a combination of dietary manipulation, medication, behavior modification, and positive reinforcement offered in a stepwise approach. Laxatives should be avoided because although they treat constipation, symptoms of encopresis may be worsened. Stool softeners are more appropriate for the management of constipation in children with spinal cord injury or MMC. Other strategies include scheduled toileting and positive reinforcement. Toileting after breakfast uses the gastrocolic reflex and, when successful, prevents soiling throughout the day. The child should be encouraged to sit comfortably on the toilet with his or her feet supported on a flat surface or stool. The child should be instructed to increase the intra-abdominal pressure by bearing down. Initially, children with MMC may benefit from a stimulant or glycerin suppository to promote reflex defecation. When this routine is unsuccessful in the management of constipation, more aggressive therapy with routine enemas or retrograde enemas should be implemented. If the combination of dietary manipulation, laxatives, bowel training, and retrograde enemas fails to control constipation and encopresis, a colostomy or antegrade continence enema procedure may be performed (109).

ANTEGRADE CONTINENT ENEMA PROCEDURE

Pediatric patients with neurogenic bowel, chronic constipation, Hirschsprung's disease, or anorectal malformations may benefit from construction of a continent stoma to manage fecal soiling. The antegrade continent enema stoma was first described by Malone in 1990 (110). Another surgical option includes a button cecostomy that allows placement percutaneously but might limit future reconstructive options (111). Minor complications are reported by many patients after insertion of the button, including cellulitis, stomal stenosis, and superficial infection at the button site (112). The stoma can be created from the appendix, from the small intestine, or from colonic segments. The appendix is the preferred bowel segment. After the cecum and appendix are mobilized, the tip of the appendix is brought out through a circular skin incision below the normal appendectomy incision (113,114) or through the umbilicus (105). The procedure is usually performed through a midline incision because of abnormal fixation of the cecum in the right upper quadrant (a common finding in children with myelodysplasia), exaggerated lordosis, and intraperitoneal adhesions from ventriculoperitoneal shunts (115,116).

The most common complications include difficult catheterization, stomal leakage, sloughing of the conduit, and stomal stenosis. Clark et al. reported that the following variables are associated with better outcomes in children with a neurogenic bowel and bladder managed with

a Mitrofanoff and/or Malone antegrade continence enema procedure: compliance with clinic visits and irrigations, younger age (< 8 yr), and smaller body habitus (117). The result is fewer complications and better urinary and fecal continence.

Patients are instructed to administer irrigant by means of a catheter in the stoma in the evening while sitting on the toilet. A cecostomy button must be irrigated daily with a small volume of normal saline to prevent clogging with stool. Patients are instructed to lavage at different intervals varying from 24 to 72 h. The volume is individualized to the patient and generally ranges from 500 to 1500 mL; evacuation takes place from 15 min to 2 h after lavage (112). Irrigant solutions vary from tap water to saline as well as laxative agents and glycerin.

Patients report improved quality of life and emotional and psychosocial well-being after the procedure because of improved continence and independence (114).

MINIMALLY INVASIVE ALTERNATIVES TO RECONSTRUCTION FOR INCONTINENCE

One of the more exciting developments in surgery for neurogenic incontinence has been the application of minimally invasive techniques. The first laparoscopic bladder augmentation was a gastrocystoplasty performed in a pediatric patient with sacral agenesis (118). Since then, most of the reported laparoscopic bladder augmentations have been performed in adults (119). The current state-of-the-art for bladder reconstruction and the antegrade continent enema procedure is laparoscopic-assisted reconstruction (107). In this technique, the umbilical stoma is prepared by creating a posterior umbilical flap and then achieving open access into the peritoneum using a radially dilating laparoscopic trocar (120). Laparoscopic techniques are then used to mobilize the cecum and appendix, mobilize the sigmoid, harvest omentum, or perform nephrectomy in preparation for an ureterocystoplasty. Happily, laparoscopy appears to be safe in children and adults with ventriculoperitoneal shunts (121). The more technically demanding reconstructive procedures can then be performed through a very small lower abdominal incision, usually a Pfannensteil. Comparison with open techniques for similar operations suggests equivalent or improved results with shorter hospital stay and time to regular diet (106).

A recent review of the largest series to date of such procedures suggests success rates equal to or better than open techniques, with a stoma revision rate of 7.7% (122).

SUMMARY

Urologic management of the patient with neurogenic bowel and bladder is aimed at maintaining normal renal function and, when appropriate, promoting urinary and fecal continence. Lifelong follow-up is necessary for these patients, whatever their management, because of the risks of neurologic deterioration, renal and bladder calculi, UTI, urinary incontinence, and renal impairment. Urologic concerns were once the most common cause of death in children and adults with MMC; now these issues can be managed with the expectation of normal renal function and urinary continence in the majority of cases.

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11 Pediatric Stone Disease

Current Approaches to Diagnosis and Management

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INTRODUCTION

Great strides have been made in the diagnosis and management of pediatric urolithiasis, in significant part because of technologic improvements in instrumentation in urology. Stones in children remain a less frequent problem compared with the adult population; however, they can be challenging to manage (1).

INCIDENCE

Stones may be seen in as many as 1 in 1000 pediatric hospital admissions in the United States, with greatest incidence in the southeastern part of the country (2). In some countries, however, pediatric urinary calculi remain a significant problem (3). Stones in infants may mimic colic. Infants who have been on prolonged diuretic therapy and have colic should be evaluated for possible stone formation (4). Preschool and older

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children typically have hematuria (5) and pain remains a symptom in only 50% of children (2).

Urinary calculi are seen more frequently in white children compared with other ethnic groups and appears to affect the sexes equally (5). The location of calculi in the urinary tract is age dependent, with younger children having renal calculi and older children having ureteral calculi (6). In some parts of the world, however, bladder calculi are endemic in children (7).

CAUSATIVE FACTORS

The causes for stone formation in children are the same as in adults. The cause may be anatomic, metabolic, infectious, or undetermined. Anatomic causes include various congenital obstructive and neurologic abnormalities. Ureteropelvic junction (UPJ) obstruction has been noted to contribute to the development of calcification in 16% of patients (8). Further investigation, however, has revealed that children with UPJ obstruction and an associated calculus have metabolic abnormalities similar to those of children who have calcification without UPJ obstruction, indicating an additive role for UPJ obstruction in the development of calculi (9,10). Additionally, patients with UPJ obstruction and coexisting calculi have a significant rate of recurrence of calculi following repair of UPJ obstruction, lending further credence to the role of metabolic factors in the development of calculi (11). The presence of posterior urethral valves and the associated reflux, bladder dysfunction, and stasis may predispose the patient to the development of bladder calculi (12,13). Vesicoureteral reflux has been felt to be a causative factor in the development of calculi (14,15) although the association seems to be more definite in those kidneys with significant scarring (16,17). Additional anatomic factors include ureteroceles and the exstrophy-epispadias complex (18). Immobilization has been noted to influence the development of urinary calcification in children, although this association is not consistently noted (18,19). Spinal dysraphism is associated with an age-related increase in the development of urinary calculi (20). These patients also had high rates of stone recurrence resulting from associated infection and lower urinary tract reconstruction (20).

Functional voiding disorders are a significant cause of urinary calculi (21). Incomplete bladder emptying, complicated by inadequate fluid intake and recurrent infections, make these children susceptible to recurrent calculi. As with other potential causes, metabolic issues may be additive factors in a subset of children with voiding dysfunction (22).

Metabolic causes remain a major cause for urolithiasis in children. Hypercalciuria is noted in almost half of all children with calculi (5).

Hypercalciuria is the end pathway for many metabolic conditions that predispose to urinary calcification (5). Children with hypercalciuria frequently have persistent gross or microscopic hematuria (23). Microcalculi have been implicated as the cause of hematuria in a significant number of patients with hypercalciuria in whom stones are not evident on radiographic examination (24). This may represent a prelude to the eventual development of renal calculi (24). Intractable hematuria in association with hypercalciuria may be managed with thiazide diuretics.

Other metabolic abnormalities associated with stone formation include primary hyperoxaluria (25) an inherited metabolic abnormality, and secondary (enteric) hyperoxaluria, which is noted in children with cystic fibrosis (26). Cystinuria accounts for 5% of pediatric urolithiasis (3,27) and uric acid stones represent an additional 2% of stones in children (3,5), although a higher incidence has been noted in patients receiving ketogenic diets for seizure management (28).

Infectious causes may be noted in 13–25% of children with urolithiasis (29,30). Urease-producing bacteria cause alkalization of the urine, with supersaturation of struvite and crystallization (13). The increased use of continent urinary pouches for reconstruction can lead to development of calculi because of deposition of mucus and inherent contamination during clean intermittent catheterization (13,31). Gastric augmentation tends to protect against stone formation (13).

In 14–20% of children with stones, no cause is identified (32,33). This usually occurs in children who have a single stone episode without recurrence. A cause can be found in most children who have recurrent stone formation.

DIAGNOSIS

A complete history obtained from the parents or caregivers that includes prematurity, diuretic or other medical therapy, family history of stones, history of voiding or elimination problems, neurologic abnormalities, and prior surgical reconstruction. Physical examination in patients not in serious distress is typically unremarkable, although evaluation of the spine for dimples or other defects is mandatory.

Ultrasonography remains the primary method used to diagnose children because stones are well-visualized using this technique (6,33). In the emergency setting in which a child has pain and hematuria, noncontrast computed tomography (CT) has replaced intravenous pyelography for diagnosis of urinary calculi (6,34). Other potential causes for acute abdominal pain can be ruled out with this single study. Once a stone is identified, follow-up can be performed with ultrasonography (33).

MANAGEMENT

Intervention is based on the size, location, and degree of urinary tract obstruction. Early institution of hydration and appropriate timed voiding regimens in patients who may have underlying voiding dysfunction are first steps in management. Miniscule calculi (< 2 mm) in the renal pelvis that do not obstruct may be candidates for follow-up because a high percentage of these pass spontaneously (6). Evidence of stone growth on follow-up should prompt intervention. Management in children with pain mirrors that in the adult population. Appropriate pain control and hydration to facilitate stone passage are the first steps. Obstructive lower ureteral calculi can be managed with primary ureteroscopic extraction (33). Alternatively, stent insertion and subsequent shock wave lithotripsy (SWL) can be used.

The initial management of nonobstructive stones should be SWL (35). Ultrasonography is used for stone localization. Even the smallest infants can be treated with SWL, although gantry modification may be necessary with older lithotripsy machines (3,35). Although parenchymal injury has been reported (36), this effect seems to be transitory and no long-term effect on function has been proven (37). Appropriate care must be taken to protect the ipsilateral lung from injury. Most patients can be treated without ureteral stenting. Many older children can be treated with sedation only. Infants usually require general anesthesia for treatment (33,35). Some centers use lithotripsy for the management of staghorn calculi in children (38). It has been postulated that the pediatric ureter may be better able to transport stone fragments (39), however, most reports of unstented SWL do include patients in whom steinstrasse and obstruction develop (40–42). Recurrent stone formation on residual fragments remains a potential long-term risk with SWL.

Immediate ureteroscopy and stone extraction for patients with ureteral calculi can be performed safely in most young children (33,43). Smaller ureteroscopes can access the pediatric ureter with minimal dilatation (43). If dilatation is necessary, this can be safely performed in children. Although reflux may be noted after dilatation, it is typically mild and does not appear to have clinical significance (43). Three-prong graspers and stone baskets are available to fit even the smallest ureteroscopes. Use of safety guidewires and short-term postprocedure stenting are recommended in all children. Stents may be withdrawn per urethra, using the string attached to most pediatric stents.

For large upper tract stones, percutaneous nephrolithotripsy (PCNL) may be the best management strategy (44,45). We have elected to manage staghorn calculi with primary PCNL. Placement of percutaneous

access can be performed by interventional radiology. We prefer to place our own access in patients without significant spinal deformity and in those with renal dilatation. In children, using of the min-perc system in conjunction with the Holmium laser will permit successful treatment of most stones (46,47). A higher potential exists for complications following PCNL; however, if the procedure is performed carefully, complications are typically minimal. The most frequently noted complication is hemorrhage (48). If bleeding is noted, the procedure should be stopped and an appropriate-sized tube should be placed rather than persisting and causing further damage. The author obtains CT scans on postoperative day 1 or 2, and if residual calculi are noted, repeat PCNL is performed at the same hospitalization. Nephrostomy tubes are left in place for 48–72 h after complete stone removal and are typically removed before patient discharge. In adolescents, PCNL is performed using standard adult instrumentation.

Few patients require open renal surgery today for stone removal (49). At our institution, open surgery is limited to those patients requiring intervention for obstructive lesions (i.e., infants with UPJ obstruction and associated intrarenal calcification).

Bladder stones may be managed transurethrally with laser or ultrasonic stone fragmentation (50). Patients who have stones in an augmented bladder or neobladder are managed with endoscopic techniques through the catheterizable channel (31,51). Large stones can be managed through a percutaneous suprapubic cystostomy that can be dilated to accommodate a nephroscope (52). Placement of the stone in an endoluminal pouch and subsequent fragmentation will prevent dispersal of stone fragments in the bladder (53). In some children with large bladder calculi, a small cystostomy incision will permit the stone to be removed intact (31).

All collected stone fragments are sent for chemical analysis. Use of appropriate antibiotic therapy accompanied by efforts to find the cause of infection will prevent recurrence of infection-based stones. Metabolic work-up for stone formation is performed 3–4 wk after complete stone-free status is achieved (54). Metabolic work-up includes a 24-hr urine collection for evaluation of calcium, cystine, uric acid, sodium, oxalate, and citrate. Serum studies include electrolyte profiles, calcium, magnesium, phosphorous, and uric acid. Parathyroid hormone levels should be obtained in children who have elevated urine calcium levels or decreased serum phosphate levels (30).

Medical management of pediatric urolithiasis includes reduction of dietary excess; however, a low-calcium diet is not recommended. Potas-

sium supplementation and reduction of sodium intake may be recommended in patients who have idiopathic hypercalciuria (55). Patients in whom hypercalciuria persists despite dietary modification are candidates for diuretic therapy (56). Magnesium, citrate, and phosphate supplementation is beneficial for the management of hyperoxaluria. Urinary alkalization is used to manage children with cystinuria and includes the consumption of methionine-rich foods (5).

Follow-up of children with stone formation includes continued monitoring for the redevelopment of calculi. Ultrasonographic evaluation every 3–4 mo for at least one year after achievement of a stone-free state is recommended.

CONCLUSION

The diagnosis and management of pediatric stones continues to evolve. Radiographic evaluation with ultrasonography and CT has replaced intravenous pyelography, reducing the potential for serious contrast reactions. Better lithotripters permit targeting and fragmentation of stones in smaller children with greater efficiency and reduced discomfort. Miniaturization of instruments allows most pediatric ureters and kidneys to be endoscopically visualized and stones to be managed successfully. Open surgery plays an increasingly limited role in stone management.

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Developmental Perspectives of Children with Genitourinary Anomalies

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INTRODUCTION

Genitourinary (GU) anomalies impact childhood development from the time of diagnosis. GU anomalies diagnosed at birth interact with all aspects of development. Parent–infant bonding, growth and development of parenting skills, psychosocial and psychosexual developmental milestones, parent–child bonding, marital relations, sibling relations, and peer relations are impacted. Family and child vulnerabilities tend to be accentuated, and coping skills are typically not innate (1). Protective factors and resiliency are present but are poorly understood at this time. GU anomalies are among the more common congenital defects, tending to be seen at birth or at least some time before puberty. Genetic and somatic pathophysiology have not been well elucidated, but sophisticated surgical and medical interventions are available. Surgical advances

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have moved faster than our understanding of the psychological consequences of both the anomalies and the surgical reconstructions. Despite the frequency of GU anomalies, there are few cross-sectional and outcome research studies regarding the significance of such anomalies on child development (2–6). Such outcome research is ongoing, but data and data analysis are incomplete (7,8).

Developmental milestones, including specific behaviors, language, cognition, and social skills, can be important markers for observing the effects of illness, surgeries, and physical conditions in children. Additionally, psychosexual developmental aspects of psychosocial development are especially important because of the relationship of both the urinary and reproductive systems to the genitalia (1,2,4–6). The relationship between mother and child is also of particular concern (9,10). Dividing childhood arbitrarily into time periods or stages may be useful for a categorical discussion of the potential psychological impact and consequences of chronic GU conditions or GU procedures such as voiding cystourethrograms or cystoscopies. Because of limitations of space, the scope of this chapter will not include discussions of resiliency and protective factors, important as they are to any aspect of development (11).

The state of research on major GU anomalies has not established a clear relationship between unusual insults and resiliency or protective factors. Additionally, it must be understood that research is incomplete in these areas, whereas the impact of chronic illnesses such as asthma or diabetes has been studied to some degree (9,10,12). Conditions with urinary or sexual ramifications have been underemphasized. In fact, normal psychosexual development has not been well studied (1,13). Aspects of this chapter must, therefore, include clinical impressions, research impressions, and anecdotal data. For general discussions of normal development and resiliency and protective factors, the reader is referred to the myriad of texts and articles discussing normal childhood development (11,14). This chapter will outline an overview of risk factors and vulnerabilities that are faced by children with major GU anomalies.

INFANCY AND TODDLER YEARS

Issues of pregnancy, labor, delivery, and postnatal health are important in the developmental history of any child. If GU anomalies are recognized before or at birth, such history may be apparent; however, the significance of perinatal anomalies or events may be less obvious (15). The effects and consequences of such GU anomalies on development at these stages are poorly documented in the literature, and the mechanisms leading to such consequences are only now beginning to be assessed (1,7).

There is likely to be a negative impact on maternal–child bonding when obvious or gross birth defects are present. Maternal guilt appears to be of increasingly recognized significance in understanding the mother’s reactions not only to the birth but also to the perinatal and subsequent requirements of the child’s conditions, including medical care, surgeries, nutrition, and aspects of chronic illness. Additionally, paternal–child bonding may be affected. Importantly, a birth defect in a child affects the parents’ relationship in unpredictable ways: long or repeated hospitalizations and multiple surgeries or procedures may stress the child and the parents and may further strain mother–father relations (15). Extended family responses and interactions can assist and improve or sometimes further complicate the overall family situation.

Such global conditions intrude on the development of the infant and the toddler because of dependence and helplessness, central nervous system (CNS) immaturity, and other organ system immaturity (16,17). In this light, it appears that chronic illness, hospitalizations, and chronic medical/surgical interventions may cause anxiety disorders or may contribute to such disorders in an already vulnerable child (14,18,19). Infants and young preschool children tend not to connect the nature of their conditions with consequences. In other words, infants and toddlers tend not to include their experience into their very existence. Such early understandings of illness are dominated by magical thinking and beliefs that mother controls their lives. The sense of self, early awareness of the self in terms of the outer world, and the sense of his or her world encompass and circumscribe the requirements and consequences of their anomalies or illnesses. Identity becomes entwined with anomaly.

The relationship between CNS development and illness, anesthetics, and surgeries is equally unclear (16,17). Yet the age of the child at the time of medical interventions strongly influences the child’s perceptions of illness (9,10). It would be expected that brain development during infancy and the toddler years, as well as during later childhood, would be impacted by such perceptions and by the illness and medical interventions themselves, although the mechanisms are unknown (16,17). Care providers must routinely assess language acquisition, psychosocial behaviors, motor development, and cognitive skills in these children. Frontal lobe development, especially in terms of executive functions, may be particularly vulnerable. Parents must be educated to look for specific developmental milestones and correlate them to typical age ranges for such development. If older siblings are present, such correlation will be easier for the parents by comparison.

Illness and medical interventions can be important in terms of acuteness vs chronicity, child's age at onset, parental and family functioning, illness prognosis, response to treatment, and complications of either the illness itself or the interventions (9–12). Chronic or long-term effects such as genital deformity, incontinence, or renal failure may not stand out in early ages. Nevertheless, parents may begin to recognize the implications for later years. The temperament of the child and the competency of the parents may crystallize toward the end of infancy and the early toddler years, revealing an evolving pattern of behaviors and responses (15). It is very important to observe such development to prevent problems or to treat psychological conditions that may be related to GU conditions.

PRESCHOOL AND EARLY SCHOOL YEARS

As children move toward school age, their understanding of illness and of medical interventions becomes more sophisticated. Cause and effect becomes a greater reality in their thought processes, and magical thinking begins to diminish, although traces of magical thinking remain until preteen years. Such greater understanding appears to increase the child's vulnerability to anxiety in general, and can result in strong anxiety reactions to medical situations and an accentuated foreboding with procedures, anesthetics, surgeries, or even medical visits (11,18). Some children become overly private with their body or genitals; others appear uninterested if someone wants to examine them or especially their genitalia. Unpredictable child reactions tend to accentuate tensions within the family and within medical situations themselves. Unpredictability lends itself to a sense of helplessness, and children tend to devolve to demoralization in the face of helplessness. Demoralization in children is seen by adults as a lack of responsibility and (appropriate) response. Parents often react to a child's demoralization by confrontation-conflict or by supervening, noticeably dividing responsibilities among themselves and other caretakers. Health care providers may learn to dread medical visits because of such conflict and lack of direction within the family.

The child, in the meantime, also begins to develop a pseudomaturity, especially in terms of verbal interactions with adults. Such pseudomaturity occurs in relation to unusual or excessive association with multiple adults (health care providers) in varying situations. The result of such development is the sense among adults that the child can comprehend more than he or she actually does and should therefore be able to respond in a more mature or predictable manner. Pseudomaturity creates misunderstandings of its own. It can impact the child's social,

academic, and home life as well, further complicating psychosocial development. In addition to a sense of personal degradation because of incontinence and other aspects of lack of mastery, the child feels further demoralized because he or she is unable to achieve the expectations of parents and other adults. Demoralization in young children often simulates or can effect a major depression.

Complications of GU conditions and the medical, surgical, and anesthetic interventions necessary can also interfere with psychosocial development simply by occupying extended blocks of time that would be otherwise allotted to more typical developmentally important social interactions. This can lead to developmental delays, especially in terms of social and academic skills and performance, and can accentuate the emotional impact of the condition itself. Many parents express concern that learning disabilities may be more common in such conditions, although there are no data. Additionally, children have limited experience in life and therefore limited coping skills: reactions and responses to procedures or surgeries tend to mimic the child's reactions to their prior procedure. Thus, if a previous surgery occurred about age 5, for example, and the child is now preparing for a surgery at age 8 yr, he or she may react much the same as at age 5. Confusing to involved adults, the pseudomature child now appears to have regressed. However, such regressive reactions are typical until early to midadolescence. Having experienced chronic illness and interventions, a child's lesser potential for learning and abstracting presents a lesser ability to correlate behavior with age. Boys may have more difficulties than girls partly because of their commonly increased activity levels coupled with lower abilities to accede to social requisites or demands.

Incontinence is common in GU anomalies and becomes a social, developmental, and adjustment obstacle to the child at least by school age. Genital anomalies may or may not be associated with incontinence. In any case, incontinence creates a growing awareness in the child of an inability to master what every other child can do: control urinary stream. This stimulates anxiety and impacts body image. If genital anomalies are also present, which is much more common in boys, body image is further insulted. Indeed, body image distortion appears to be a common and often serious problem in children with GU conditions (2–7). Children may develop a complex sense of loss of autonomy, of normalcy, and of sameness (i.e., not being different). Self-perception as well as identity itself takes on a sense of being ill, or rather of being different: “I am an exstrophy child,” for example, instead of “I am a girl or boy with varying attributes who also has exstrophy.” Identity issues are

indeed important. Many children with significant GU anomalies seem to wear differentness as a scarlet letter. Without pertinent or sometimes poignant questioning, such children may be able to gloss over or conceal such feelings from the busy clinician.

Growing sensitivity can be recognized in many of these children in their early school years. Such sensitivity manifests itself quite obviously in terms of ease of succumbing to teasing, for example about wetness, or of being easily offended. These are painful experiences for such children and seem to be felt with more intensity and dread than for typical children. On the other hand, by the time these children are about 7 or 8 yr old, they may be more sensitive to the pain of other children or even of adolescents or adults. This sensitivity often is pervasive among children with significant GU anomalies. Recognizing it and adapting to it can be important techniques to bolster a child's self-esteem, and in later years, to alter the sense of differentness to a sense of being special.

PREADOLESCENT YEARS

Psychosexual development is of particular importance during this period. Psychosexual developmental obstacles can be recognized with careful observation in the preschool to early school years by trained personnel. In preadolescent years, such obstacles are apparent in the taking of a general history. Specific questions about psychosexual behaviors, attitudes, and anxieties will elicit from these children a wide array of important clinical data. Perhaps as the result of incontinence or of genital anomalies that require surgical reconstructions and frequent examinations, children most commonly reveal psychosexual developmental obstacles by the nontouching of the genitalia. Typical children touch, rub, examine, and otherwise stimulate their genitalia from late infancy through mature years, modulated variably by family, religion, or other social values. Children with genital anomalies and genital surgeries are more likely to avoid contact with or recognition of their genitalia. In preadolescent years, they can and often do reply to appropriate questions that they dislike or even hate their genitalia (7,8). Although the implications of such negative genital self-esteem are unclear, such feeling would appear to be highly clinically significant even if only because such statements are so rare in typical child and adolescent development.

If incontinence is present, self-esteem will continue to lag behind peers in overall development. Again, body image and genital image appear to be significantly affected and affects overall development. In this age group, however, peer relationships appear to be more affected

than in earlier years. Psychosocial development tends to lag somewhat behind peers, and social and even sexual experimentation typically tends to lag, often markedly. Thus, the sense of femaleness or maleness develops inadequately and effects additional inadequate psychosexual development. Relationships with same-sex and opposite-sex peers are impacted by this sense of gender or genital ineptness. Many of these children relate or profess an unwillingness to participate in many social activities beyond those that might lead simply to discovery of incontinence or their other anomalies.

Indeed, discovery is an issue of great importance to these children (7,8). Privacy is of utmost concern; these children do not want any of their perceived anomalies to be known by anyone outside the family. Yet secrecy is not only not necessary, it is also likely to be counterproductive to normal development. In other words, the children may well be capable of and even interested in discussions of their bodies, their pathophysiologic problems, and the ensuing social ramifications, with their parents or with an interested third party. However, they are very unlikely to tell any other person about their incontinence or genital anomalies. Psychosexual developmental vulnerabilities appear to supersede their psychosocial vulnerabilities beginning in this age group. Privacy is vital; secrecy is unnecessary.

The emotional disconnection between the child and his or her genitalia is not only pronounced at these ages but portends greater emotional psychosexual and sexual problems for the future. By the ages of about 11 or 12 yr, many of these children begin to recognize the future sexual implications, although they generally would not consider any sexual activity at this time. Again, sexual exploration and experimentation is virtually absent or amazingly clandestine in the vast majority of these children, even self-exploration. Such developmental obstacles influence general psychosocial development broadly.

THE DYNAMICS OF EARLY ADOLESCENCE

Early adolescence, that is the onset and progression of puberty or the attainment of ages about 13 or 14 yr even without puberty (although generally after adrenarche), initiates the gradual merging of psychosexual drives and meaning, with broader psychosocial themes and social integration. Thus, sexual drives typically have more global goals than mere orgasm or desires to be with the in boy or in girl; children begin to recognize specific patterns of sexual attraction, including not just sex-of-orientation but also narrower categories of body habitus, for example, or hair and skin color. Orgasm, for example, as a CNS drive

or desire begins to couple and interlock with specific fantasies and imagery related to a child's specific attractions. This signals the developmental foundations of later broad-based and complex social and sexual interactions and ultimate long-term relationships. The evolving complexity of satisfactory relationships depends on a gradual integration of simpler but crucial relationships and recognitions.

Developing successful simpler relationships during these early years is difficult for children with GU anomalies because of their inability to recognize or achieve early goals and needs of sexual-CNS development and their inability to accept the potentially pleasurable and developmentally necessary tasks of genital self-contact and self-awareness. Of interest is that most young adolescents have variable anxieties about their psychosexual development and how to integrate psychosexual into psychosocial developmental tasks. However, the vast majority of children proceed with social development in spite of these anxieties and rather uncommonly discuss such feelings or worries with parents or with outside professionals or even peers. Of great clinical and developmental significance is that for children with major GU anomalies the degree and intensity of these kinds of anxieties is striking. Indeed, particularly in boys, these anxieties result in many aspects of psychosexual development and various sexual behaviors to be absent; these adolescents become developmentally blocked.

Needless to say, deficits in the merging of psychosexual and psychosocial developmental directions and tasks delays overall social development. This is not limited necessarily to sexual relationships or sexual attractions; it often also affects same-sex relationships, especially insofar as femaleness or maleness may be emphasized in particular peer and other social interactions. Thus, the child is faced with two developmental hurdles: one is the social and sexual aspects of psychosexual drives and interests, and the other is the social aspects of dealing with same-sex activities or interactions.

MIDADOLESCENCE AND THE BROADENING OF PSYCHOSOCIAL AWARENESS

The midadolescent period is a developmental admixture of great hormonal stimulation; enlarging body size; growth in the breadth and depth of insight, judgment, and abstracting abilities; and the recognition of changing and maturing relationships with adults and peers. Simultaneously, midadolescents experience a sexual drive that at times can be seemingly almost uncontrollable. Sex drive itself may occasionally get in the way of relationships or other aspects of social

development. Overt as well as covert sexual exploration or even experimentation commonly begins during these years and is often complicated by other simultaneous social experimentations. Typical midadolescents may get into difficulties with adults or parents because of poor judgment and inflicted insight, and learning from mistakes can be a major manifestation and consequence of midadolescent behaviors. Preliminary evidence implies that many children with GU anomalies bypass some of this inflicted insight because of delays in psychosocial development.

Mood and anxiety disorders can be a problem for any midadolescent, further complicating the pressures and demands of a rapid developmental period. Adolescents with GU anomalies display additional vulnerabilities to anxiety disorders and probably to mood disorders (7). Anxiety disorders appear to be pervasive. Such disorders can range from significant anxiety related to medical or surgical procedures or illness to far more generalized and pervasive forms of anxiety. Sometimes in these age groups, anxiety disorders and mood disorders can be difficult to differentiate, but a common manifestation is irritability, especially with family and adults. Irritability with peers and friends may indicate more complex illness or depth of illness. Seeming changes in personality or significant changes in behavior, academic performance, or social interactions are a strong indication that psychological or psychiatric assessment and possible intervention is needed. Psychiatric disorders during this period can be quite harmful, possibly introducing a new set of potential social deficits (10–12,14). Further research in these areas is ongoing (7,8).

PSYCHOSOCIAL IMPLICATIONS FOR LATE ADOLESCENCE: CRITICAL INTERVENTIONS

Late adolescent development is, of course, built on successful maneuvering from the child's earlier developmental trajectory: prior obstacles engender future deficits. Because late adolescence is a time of very dynamic psychosocial interactions on multiple levels, obstacles preclude typical development and create more mosaic social outcomes. Sophisticated mature mastery may be interspersed with immature and underdeveloped potential. This is particularly apparent when observing sexual development and sexual interactions and relationships in these children, although close observation will reveal other social deficits as well.

Mastery of adult coping strategies may alternately obscure or assist with developmental tasks in most social arenas (2–4,6,7); psychosexual

development, however, tends to lag fairly far behind. These children often begin to explore their psychosexual and sexual inadequacies more realistically at this time and are often quite open to evaluation and assessment as well as to proposed interventions. As their ability to integrate social and sexual development improves, their potential to work around their deficits improves.

Health care providers should direct attention at the verbal potential and verbal spheres of these older adolescents (20). Verbally they are quite sophisticated and may use their mastery of verbal abilities to gloss over or hide emotional inadequacies; however, their comprehension tends to be quite sophisticated as well. Therefore, we must recognize the significance of verbal intimacy. With some instruction from the caregiver, the adolescent can recognize and subsequently verbalize his or her intimate anxieties. With a little education, the adolescent is likely to discuss the fears and anxieties and the deficits and loneliness he or she experiences, all of which are of a remarkably intimate nature. With education and practice, albeit initially only with the caregiver, the adolescent will learn to discuss his or her social and sexual fears and deficits with a chosen or possible mate. Health care providers must carry the responsibility for initiating these discussions because it is unlikely that most adolescents will initiate such topics on their own. Therefore, providers must overcome their own embarrassment about dealing verbally with such intimate subjects.

A cognitive behavioral therapeutic approach is likely to be the most efficacious intervention for most of these adolescents because of their verbal abilities and their long experience with adults. Such approaches use the adolescent's cognitive skills and personality style to design and select specific strategies for the child's chosen specific goals or identified problems, generally one or two problems at a time. Each coping strategy requires practice and fine-tuning before the adolescent is good at it and before he or she shows significant improvement. Strategies the child cannot accept or will not perform are cast out.

Sexual counseling, in addition to psychological counseling, will be necessary for many of these adolescents. Specifically, girls might sometimes wonder (often during early to midadolescence) if the vagina is physically open or if it will be able to handle an erect phallus; girls might wonder if they will be able to get pregnant, carry a baby, or deliver a baby. Similarly, boys might need counseling about sexual positions, for example, to maximize the function of a short erect phallus or to minimize discomfort to them or to their mates; such questions often arise during midadolescence.

SUMMARY

The dynamic aspects of growth and development and of social and sexual interactions from infancy through late adolescence hold a special importance for children with major GU anomalies. Dynamic interactions and experiences imply variable and sometimes unpredictable responses and reactive development. Research and clinical impressions as well as rather substantial anecdotal data strongly indicate that the perceived meanings of such GU anomalies have powerful implications for psychosocial development, especially as it is impacted by psychosexual development and consequential developmental impairment. Developmental milestones can be impaired or even missed. In infancy, these may relate to maternal–child bonding, and in late adolescence they may relate to difficulties with social and sexual relationships.

Dynamic growth and development continues in such children despite developmental obstacles, but variable developmental trajectories are the rule. Many such trajectories are considerably skewed, veering markedly from the developmental trajectories of typical children. The patient role, hospitalizations, anesthetics, and medical/surgical interventions affect development in unpredictable ways that vary from child to child, yet patterns of development are common relative to specific GU anomalies. A difficult infancy has important ramifications for toddler years, preadolescent difficulties suggest problems for adolescent years, and so on. These children's vulnerabilities interact with innate protective mechanisms and resiliency, impacting and directing future development. Therefore, although similar experiences and problems may lead to some similar outcomes, a specific child can only fall within a much larger range of behaviors, attitudes, emotions, and reactions.

Problematic development requires dynamic and sophisticated interventions. Specific interventions must be tailored to the specific needs and strengths of a given child or adolescent. Many interventions will be of a cognitive nature and will require practice by the child and adolescent. Successful interventions for psychosocial developmental impairment may not correct all deficits. Nevertheless, adults may be happy with the child's ultimate developmental achievements; humans are remarkably adaptive even in the face of significant childhood developmental impairments. However, a satisfying and mentally healthy childhood would seem desirable for all. Success, therefore, is measured by the late adolescent's and adult's observations of his or her own satisfaction with life. Our goal is to improve the developmental trajectory for the child and

the adolescent to further improve adult development and adaptation and mirror the improvements in surgical and medical care. It remains for outcome studies to determine whether such success improves with active psychological and developmental interventions throughout the life story and what specific interventions are most efficacious.

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13 Pediatric Genitourinary Oncology

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INTRODUCTION

Substantial advancements have been made in the treatment and survival of children with genitourinary cancer over the past 50 years. No better evidence of this is the outstanding survival enjoyed by a large number of patients with Wilm's tumor. These improved outcomes are largely the result of multimodal therapy utilizing chemotherapy, radiation, and surgery. Advancements may also be attributed to an organized approach to research and patient care.

With the advent of molecular medicine, the field of cancer therapy appears ripe for new understanding. For example technology such as microarrays may allow for the "molecular staging" of patients. New insights such as these, together with the collaborative care and investigation organized by Children's Oncology Group (COG) and others, have poised the field to make significant advances in the near future.

This chapter reviews the current understanding of the pathogenesis and treatment of patients with genitourinary rhabdomyosarcoma (RMS), Wilms' tumor, and neuroblastoma (NB). We also discuss recent findings and future directions of study and treatment.

RHABDOMYOSARCOMAS

Background

Rhabdomyosarcomas may develop in any part of the body that contains embryonal mesenchyme. RMS is the most common soft tissue sarcoma accounting for 50% of all soft tissue sarcomas of childhood. This represents 5–15% of all solid malignant tumors in children (1). The reported annual incidences of this tumor in the United States are approx 4.4 million in white children and 1.3 million in African-American children. There is a slight male–female preponderance (2).

History

RMS was first described in 1854 by Wiener (3). However, little was published on the treatment of RMS until the 1950s (4). Subsequently, a histological classification was outlined by Horne and Enterline that has served as the basis of the system that is widely used today (5). As with most solid tumors, surgery represented the mainstay of therapy until it was shown that the outcomes of patients with RMS improved with radiotherapy and subsequently chemotherapy in addition to radiotherapy (3,6).

By the early 1960s, Pinkel and Pinkren had demonstrated that outcome was improved further by complete surgical removal followed by chemotherapy and radiotherapy (7). The demonstration of the utility of

multimodal therapy catalyzed the formation of large multicenter trials, conducted by the International Rhabdomyosarcoma Study (IRS) group, and the International Society of Pediatric Oncology (SIOP). These cooperative groups have sought to further refine treatment, improve outcomes, and limit morbidity.

The IRS Studies

In IRS protocols, pelvic RMS is confined by definition to tumors of the bladder, prostate, uterus, vagina, and adnexa. I limit this discussion to tumors involving these sites. It is understood that it is often difficult to determine the site of origin of a large tumor that involves both the bladder and prostate. Tumors arising from the retroperitoneal space within the pelvis are not included in the IRS classification of pelvic tumors and neither are paratesticular tumors. Therefore, these are not addressed in this chapter.

In IRS-I (1972–1978), no distinctions were made based on the site of origin or on different forms of chemotherapy. During this initial study, many of the patients underwent primary anterior exenteration. Patients who received up-front surgery, followed by radiotherapy and chemotherapy, had relatively favorable outcomes. During the later years of IRS-I many patients received a trial of primary chemotherapy, albeit limited in duration. Review of the overall survival rates for patients in IRS-I with pelvic tumors, excluding the worst clinical group, shows that an overall survival rate of 75% was accomplished. It is noted that this survival rate was attained as a consequence of many radical exenterative procedures (8).

During IRS-II (1979–1984), patients with RMS received chemotherapy and/or radiotherapy prior to surgery. The initial hope that patients receiving primary chemotherapy would lessen the number of patients requiring exenterative surgery or radiotherapy was not realized in this study (9). Only about 10% of patients achieved relapse-free survival with chemotherapy alone, the majority required adjunctive radiotherapy for treatment. Overall survival was reported at approximately 80%, not significantly improved over IRS-I. The survival rate with an intact functional bladder in this study was only 25%. In a similar study carried out by the SIOP, which also advocated primary chemotherapy, less than 30% of patients had a functional bladder 3 yr out from initiation of the study protocol.

The IRS-III study was conducted from 1985 to 1992. In this study, several additions to the original regimens made significant improvements in survival. Specifically, the chemotherapy regimen was standardized to include *Doxorubicin* and *Cis-platin*. Additionally, the timing of radio-

therapy was fixed at 6 wk after the induction of treatment. Finally, IRS-III incorporated the use of primary and secondary partial cystectomy in addition to exenterative procedures. The results of IRS-III showed a significant survival advantage over those of IRS-I and II. Furthermore, the proportion of patients who retained bladder function at 4 yr from diagnosis rose to approx 60%. This IRS study showed that conservative surgery after primary chemotherapy in the absence of radiation could produce excellent disease-free survival and reduce morbidity (10).

IRS-IV included a plan to evaluate the utility of pretreatment staging using a tumor node metastasis (TNM) staging system. Chemotherapy was based on TNM stage but radiotherapy was given 9 wk later based on the original IRS grouping system, which in turn had been based on a prior IRS staging system. Hyperfractionation of radiotherapy would be evaluated, as well. Preliminary results from this study are already being reported and are discussed later in the chapter.

Finally, the IRS-V protocol is designed to evaluate patients based on stratification into low-, intermediate-, and high-risk protocols. The low-risk protocols are unchanged from previous IRS studies but new protocols are in place for intermediate-risk and high-risk patients. Patients with intermediate-risk RMS will undergo therapy using a new chemotherapeutic agent, *Topotecan*, and patients on the high-risk protocol will receive *Irinotecan*.

CAUSATION

The etiology of RMS is not thoroughly understood but it is thought to be multifactorial. Both congenital and environmental factors have been identified and it is expected that further analysis of the genome will identify specific genetic factors that predispose to this disease. A genetic etiology is suggested by the association of RMS with multiple other syndromes such as Li-Fraumeni syndrome, neurofibromatosis, and basal cell nevus syndrome (11–13). Families with Li-Fraumeni syndrome suffer from a variety of malignant diseases, including other sarcomas, breast carcinoma, brain tumors, adrenal carcinoma, and leukemia. This may be due to the association of Li-Fraumeni with loss of the tumor suppressor gene *p53* which is located on the short arm of chromosome 17 (14). Similarly, mutations of *p53* have been identified in 10% of patients with RMS (15). These patients are also at significant risk for secondary malignancies independent of their treatment for RMS.

Several environmental factors have been associated with RMS. These currently include herbicides, marijuana, cocaine, and maternal alcohol

ingestion. In addition, a maternal history of radiation and prior stillbirth seems to also increase the risk of tumor in the fetus (16,17).

PATHOLOGY

The most common sites for pelvic RMS are the prostate, the bladder, and the vagina. Grossly, RMS tend to be nodular, firm, and well-circumscribed, although microscopically they may infiltrate extensively into adjacent tissues. Endoscopically, the tumors can present as a nodular mass emanating from the prostate or bladder, often times in the area of the trigone. No other specific gross pathologic features are present except in the case of sarcoma botryoides. This subtype primarily arises in hollow organs, typically the vagina or bladder, and usually presents as a cluster of grapes prolapsing from the orifice of the hollow viscus.

The original histologic classification of Horne and Enterline included four different pathologic subtypes (*see* Table 1): embryonal, alveolar, pleomorphic, and undifferentiated (5). This classification is still widely used today. Embryonal RMS is the most common subtype seen in children. Morphologically, the tumor resembles fetal striated muscle correlating to a gestational age of 7 to 10 wk. The composition is mainly that of spindle-shaped cells with a central nucleus in an eosinophilic cytoplasm. Thirty percent of specimens exhibit cross-striation (18). Sarcoma botryoides represents a subtype of embryonal tumor. As a group, the embryonal type comprises roughly 66% of genitourinary RMS and 50–60% of all RMS in children (2).

The alveolar subtype is the second most common subtype comprising approx 15–20% of RMS. It is seen most often in older children and histologically resembles 10–21 wk gestational age-striated muscle. Specific histologic features include clusters of small round cells adhering to fibrosepta, giving the appearance of well-defined alveolar spaces. Unlike the embryonal subtype, cross-striations are uncommon. Alveolar is more often seen in the extremities and trunk.

The third most common histologic subtype of RMS is the undifferentiated subtype. These tumors are often very difficult to identify as they are made up of primitive small round cells and can be confused with Ewing's sarcoma. Unlike in Ewing's sarcoma, however, these cells arise from soft tissue rather than from bone. They can, therefore, be differentiated from the cells of Ewing's sarcoma by identifying expression of specific muscle proteins such as actin, myosin, desmin, and myoD (19,20). Additionally, the utility of electron microscopy to identify Z bands associated with actin-myosin bundles has been documented (21).

Table 1
Histologic Classification of Genitourinary Rhabdomyosarcoma

<i>Histology</i>	<i>Prevalence</i>	<i>Characteristics</i>
Embryonal	60–80%	Spindle ± round cells Loose matrix 30% striations
Alveolar	15–20%	Small round cells on fibrous septae Rare striations
Pleomorphic	1%	Varied cell shapes and sizes
Undifferentiated	5–10%	Small round cells Z-bands on EM Immunohistochem ID

Table 2
Outcomes for Rhabdomyosarcoma Based
on Histologic Classification

<i>Histology</i>	<i>Prognosis</i>	<i>5-yr survival</i>
Sarcoma botryoides spindal cell	Favorable	90%
Embryonal pleomorphic	Intermediate	65–75%
Alveolar undifferentiated	Unfavorable	40–55%

Histologic classification has been correlated to outcomes in RMS and this is summarized in Table 2. RMS can spread by local infiltration, lymphatic, and hematogenous routes. Spread to local or regional lymph nodes is present in approx 20% of patients at diagnosis (22). Distant metastatic spread occurs most commonly to the lung, marrow, and bone. Omentum is sometimes involved while metastases to other viscera, such as the liver, are rare as are metastases to the brain (23–25).

PRESENTATION AND EVALUATION

The initial presentation of pelvic RMS varies based on the organ of origination. With bladder or prostate involvement, urinary tract obstruction causing urinary retention, incontinence, or infection is often the initial symptom. Hematuria results when the tumor breaks through the mucosal layer of the genitourinary tract. Vagina tumor may present with a bloody discharge or the child may present with a mass lesion coming through the vaginal opening, as in sarcoma botryoides. RMS located at other pelvic sites may not be found until they become quite large, when significant local spread has already occurred.

Table 3
Preoperative Evaluation for Patients
with Rhabdomyosarcoma

<i>Patient evaluation</i>
History and physical, size lesion
CBC c diff
Urinalysis
Electrolytes, Cr, Ca, PO4
Alk. Phos., LDH, Bili, SGPT
Marrow aspirate
CXR
MRI
Chest CT
Head CT or MRI
CT or US of retroperitoneum and liver
Bone scan
CSF cytology
CBC, complete blood count; SGPT, serum glutamic-pyruvic transaminase; MRI, magnetic resonance imaging; CT, computed tomography; US, ultrasound; CSF, cerebrospinal fluid.

Distant spread exists in 25% of patients at the time of presentation and occasionally patients may present with systemic signs of malignancy (24). In these patients, a physical examination commonly fails to reveal a mass and one must rely on imaging to identify the location of the tumor.

The IRS-V study protocol includes a preoperative evaluation checklist (see Table 3). Although no specific biochemical markers have been identified for RMS, it has been noted that some patients may have an elevated creatinine kinase.

Radiologic Evaluation

Diagnostic imaging in patients with RMS needs to be performed in an accurate, reproducible way so that sequential imaging studies can be used to assess the efficacy of primary chemotherapy. Although the first study to detect a mass is often an ultrasound, the IRS-V protocol calls for imaging of the lesion with magnetic resonance imaging (MRI) or computed tomography (CT) scan. Fine cut cross-sectional imaging should be performed with and without contrast and accurate tumor

measurements should be taken along two axes. With regard to the assessment of regional lymphadenopathy, a CT of the retroperitoneum using thin cuts is the study of choice.

Chest imaging is needed to exclude pulmonary metastases. A chest CT is indicated if lesions are seen on plain film or if skeletal, marrow, or cerebrospinal fluid evaluations are positive, although some authors argue that chest CT should be performed in all cases (21).

Additional Diagnostic Procedures

Bone scan evaluates the patient for skeletal metastases, and aspiration can identify invasion of the marrow. Additionally, because of the toxic affects of chemotherapeutic regimens on cardiac musculature, an electrocardiogram or an echocardiogram are often recommended prior to initiating therapy. Imaging of the brain is not required for tumors limited to the genitourinary system.

Endoscopic Evaluation and Biopsy

It is important to obtain an accurate histologic diagnosis prior to proceeding with treatment. Endoscopy of the bladder or vagina and/or uterus can aid in diagnosis. An endoscopic biopsy may be performed using a pediatric resectoscope or cold cup biopsy forceps. It is important to note that use of a resectoscope loop may damage the tissue specimen and make it uninterpretable. Low cutting current should be used (26).

If endoscopy reveals no mucosal abnormality appropriate for biopsy, but an intra-abdominal mass is present, needle or open biopsy may be indicated. Although some authors have described percutaneous Tru-Cut needle biopsy as an excellent methodology for diagnosis, needle track seeding is a potential complication. If percutaneous diagnosis is not possible, or not desirable, formal laparotomy may be required for biopsy. If laparotomy is performed, a preliminary evaluation of the regional lymph nodes should be performed as well (*see* Table 4 for listing of nodal basins).

STAGING SYSTEMS

Two different staging systems are currently in use for patients with RMS. The IRS group has traditionally used a postsurgical staging system and SIOP has used a pretreatment TNM system. IRS-V calls for an evaluation of the pretreatment TNM staging system. Both systems as presented in the IRS-V study are listed below (*see* Tables 5–7).

Table 4
Nodal Basins for Genitourinary Rhabdomyosarcoma

<i>Site of primary</i>	<i>Regional nodal basin</i>
Bladder/prostate	Pelvic + retroperitoneal nodes at or below level of renal AA
Uterus/cervix	Pelvic + retroperitoneal nodes at or below level of renal AA
Paratesticular	Pelvic + retroperitoneal lymph nodes at or below level of renal AA
Vagina	Inguinal, retroperitoneal + pelvic nodes at or below common lines
Vulva	Inguinal nodes
Retroperitoneal/pelvis	Pelvic and retroperitoneal nodes
Perianal/perineal	Inguinal and pelvic nodes, may cross midline

AA, arteries.

Table 5
Tumor Node Metastasis (TNM) Classification
for Rhabdomyosarcoma

<i>TNM system definitions for rhabdomyosarcoma</i>	
Tumor	T1: Confined to site of origin (a) \leq 5 cm diameter (b) $>$ 5 cm diameter T2: Extension into/fixed to surrounding tissue (a) \leq 5 cm diameter (b) $>$ 5 cm diameter
Regional nodes	N0: Not clinically involved N1: Clinically positive Nx: Node status unknown
Metastasis	M0: Free of metastasis M1: Metastasis present

TREATMENT

Initial treatment of patients presenting with RMS should address any symptomatic issues. Specifically, if urinary obstruction is present, urethral catheterization should be performed. If ureteral obstruction is present, stent placement and/or percutaneous nephrostomy should be

Table 6
IRS Classification System for Rhabdomyosarcoma

<i>Traditional IRS group classification</i>	
Group I	a) Localized disease, complete resection: Confined to muscle/organ or origin; beyond muscle/organ of origin
Group II	b) Regional disease, grossly resected: Node negative but microscopic residual; node positive, no residual; node positive with microscopic residual +/- node most distal to primary found with disease
Group III	c) Gross residual disease: After biopsy, after attempted resection
Group IV	d) Distant disease

IRS, International Rhabdomyosarcoma Study

Table 7
Revised Pretreatment Tumor Node Metastasis (TNM) Classification

<i>Pretreatment staging classification (based on TNM)</i>					
<i>Stage</i>	<i>Site</i>	<i>T</i>	<i>Size</i>	<i>N</i>	<i>M</i>
I	OrbitHead/neckGU (other than bladder/prostate)	T1 or T2	(a) or (b)	No or Nx	Mo
II	Bladder Prostate Extremity Intracranial Trunk Intrathoracic Retroperitoneal Biliary Perineal	T1 or T2	(a)	No or Nx	Mo
III	Same and stage II	T1 or T2	(a) or (b)	N1 and N	MoMo
IV	Any	T1 or T2	(a) or (b)	Any N	Mi

performed prior to beginning therapy. Currently, the initial therapeutic approach involves up-front chemotherapy with evaluation for response. If complete response is obtained, further chemotherapy is indicated. If only a partial response is obtained, local excision is performed. Complete excision is followed by more chemotherapy; incomplete excision warrants both radiotherapy and additional chemotherapy. This basic outline is presented in algorithm form (*see* Fig. 1).

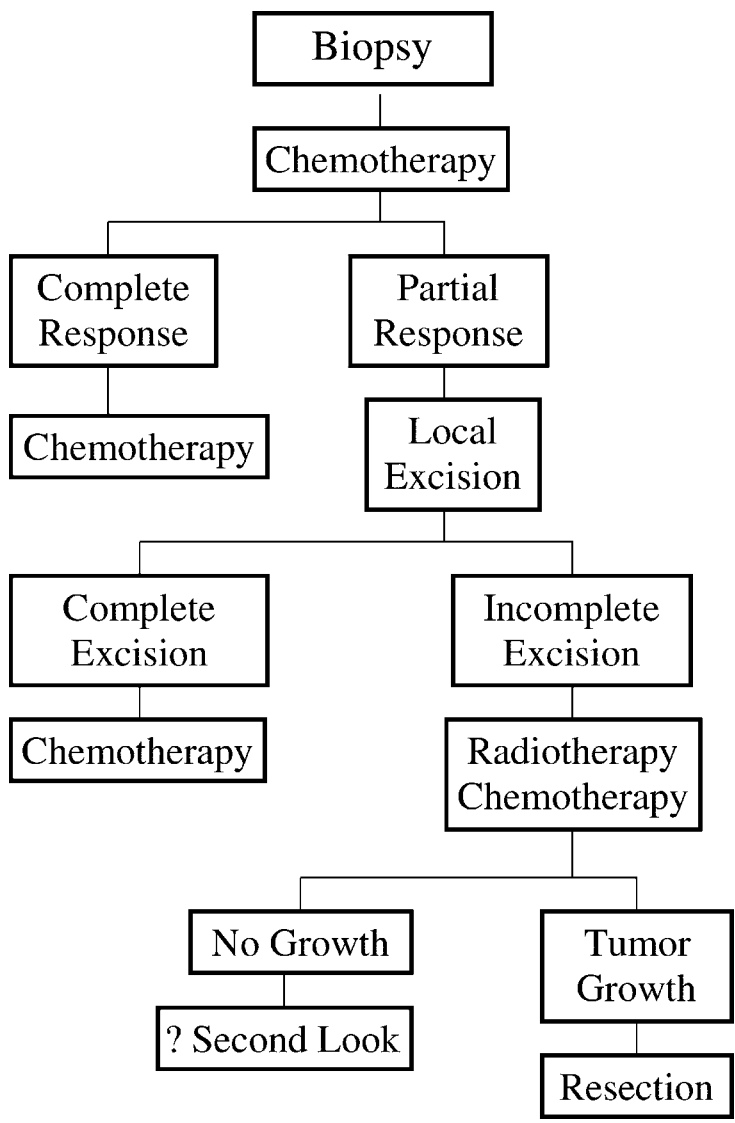


Fig. 1. Management scheme for genitourinary rhabdomyosarcoma.

Risk-stratified treatment protocols are outlined in IRS-V. For patients with low-risk RMS, initial treatment consists of actinomycin (AMD) x 1 and vincristine (VCR) x 3 for 3 wk. Low-risk patients with nonalveolar or nonundifferentiated sarcoma will continue on AMD and VCR for 45 wk. Those with alveolar or undifferentiated sarcoma will be switched to

Vincristine, Actinomycin D, and Cyclophosphamide (VAC). Low-risk patients with no residual disease after chemotherapy will receive no radiation therapy (XRT). Those with microscopic residual disease (clinical group II, NO) will receive 36 Gy given once daily, Monday through Friday, in 20 fractions of 1.8 Gy, beginning at week 3 after the second dose of AMD.

Patients with tumor involving the regional lymph nodes receive radiotherapy based on the intermediate risk protocol. In IRS-V, patients with intermediate risk RMS are randomized to receive VAC vs VAC alternating with Vincristine, Topotecan, and Cyclophosphamide (VTC). Induction chemotherapy lasts for 12 wk and surgical evaluation occurs after four courses of chemotherapy. For local control, VAC with XRT for gross microscopic residual disease with a second look operation is performed at week 24. In group 1 and group 2, VAC/VTC with XRT for gross microscopic residual disease is given and a second look operation, is performed at week 24. Continuation chemotherapy occurs from 25 to 40 wk with either VAC or VAC/VTC.

IRS-V patients in the high-risk group will participate in an “up-front study” of Irinotecan (CPT-11) followed by multimodal, multiagent therapy. These patients are known to have metastatic disease so the principle of completely resecting the initial primary tumor is less applicable. In this study, all patients will receive an initial Irinotecan window given at weeks 0, 1, 3, and 4, and will be re-evaluated again at week 5. If there is clinical evidence of disease at week 3, patients will go to a treatment schedule including VAC. If disease progresses, or there is no response at week 5, patients will go to a protocol of VAC only. Patients exhibiting a partial or a complete response will alternate VAC with Vincristine and Irinotecan at week 6. Radiation therapy is given to these patients at weeks 15 to 22 and continuation therapy lasts through week 44.

Second look surgery is applicable in select cases of RMS. Patients who exhibit an initial partial response to chemotherapy and in those who have residual disease after initial surgery, second look procedures are typically performed after further treatment with chemotherapy or radiotherapy.

OUTCOMES

Overall, survival for patients treated for pelvic RMS has increased steadily from 30% to more than 80% since the 1970s (27). This has largely been due to improvement of chemotherapy agents. Survival by pathologic subtype is presented in Table 2. As survival has improved, current protocols strive to reduce morbidity.

Bladder preservation has become a primary goal of the IRS trials. A review of recent IRS data reveals that of 109 patients with prostate or bladder RMS, 50% retained their bladders. Limited follow-up on some of these patients indicated that 75% had normal bladder function. The determination of normal bladder function, however, did not involve cystometry and has been called into question. In a much smaller series, from the Great Ormond Street Hospital in London, a significant number of patients who were studied with cystometrograms had abnormal bladder function. The use of radiation is a risk factor for bladder dysfunction as are some of the alkylating agents. Preliminary data from IRS-IV suggests that significant bladder morbidity occurs despite recent refinement of therapy. Future studies should focus on careful evaluation of bladder function in patients with pelvic disease. Other complications that can ensue in patients treated for RMS include nephrotoxicity (44), cardiotoxicity, sexual dysfunction, and infertility.

FUTURE DIRECTIONS

Recently, several important advances in the understanding of the molecular pathogenesis of this tumor have been made. Specifically, Sorenson and co-workers reporting for the COG have documented the importance of *PAX3-FKHR* and *PAX7-FKHR* gene fusions in patients with alveolar RMS (ARMS) (28). These authors evaluated the gene fusion status of 171 patients enrolled in IRS-IV, 78 of whom had alveolar histology. They found that these gene fusions are specific for ARMS and that fusion status in these patients appears to be an important prognostic indicator. In patients with metastatic disease, *PAX3-FKHR* fusion resulted in a significantly higher rate of relapse and death. Patients with *PAX3-FKHR* fusion also seemed to have a greater predisposition for bone marrow metastasis. The authors speculate that the *PAX3-FKHR* oncoprotein may confer a survival advantage to tumor cells such as resistance to chemotherapy in ARMS. Gene fusion evaluation will likely become standard in the evaluation and risk stratification of patients with RMS.

Genetic analysis of RMS has identified some common alterations seen in this tumor. These include the previously mentioned *PAX3/7-FKHR* fusion, expression of regulatory factors such as MYOD1 and Myogenin, retinoblastoma pathway mutations, and *p53* pathway mutations (29). However, until recently which individual or combined alterations could cause cell transformation was unknown. Sharp et al. have reported that transgenic mice expressing inactivation of cyclin-dependent kinase inhibitor/alternate reading frame (*INK4a/ARF*) associated with altered *c-MET* signaling undergo spontaneous development of RMS (30).

Deletions of *INK4a/ARF* have an effect on both retinoblastoma and *p53* pathways that are known to be important in RMS. Hepatocyte growth factor/scatter factor (HGF/SF) is the ligand for *c-MET* receptor tyrosine kinase oncogene. Mice with inactivated *INK4a/ARF* that overexpress HGF/SF were found to almost uniformly develop RMS with high penetrance and short latency. This important discovery begins to unravel the molecular basis for RMS as well as provide a unique animal model for investigators.

Other more broadly applied anti-cancer strategies are being evaluated in RMS as well. For example, anti-vascular endothelial growth factor (VEGF) antibodies have been shown to have a dramatic effect on RMS growth in animal models (31). The role of VEGF and other pro-angiogenic molecules such as, basic fibroblast growth factor (bFGF) and Interleukin-8 are currently being explored (32). As our understanding of the molecular events involved in RMS progresses we will hopefully see progress in this poorly understood malignancy.

WILMS' TUMOR

This tumor bears the name of surgeon Max Wilms who, in 1899, proposed that the various elements of this renal tumor were derived from the same cell. Also known as nephroblastoma, it is the most common renal malignancy of childhood. Treatment of this tumor is one of the great success stories in cancer therapy.

Approximately 450 to 500 cases of Wilms' tumor are reported annually in the United States (33). It represents approx 5% of the childhood cancers in the nation. The incidence in boys and girls is equal. The majority of patients who present with Wilms' tumor are less than 6 yr of age (34).

In large part, the success of Wilms' treatment has resulted from the collaboration of different disciplines, including surgery, oncology, and radiation therapy. These various specialties united to explore the treatment of this malignancy as the National Wilms' Tumor Study Group (NWTG) in the late 1960s. A summary of the advances made by this collaborative group bears mention. The initial NWTG trials began in 1969 with NWTG-I. This was followed by NWTG-II, which ran from 1974 to 1978. From these two studies, substantial information was obtained about the treatment of patients with Wilms'. Specifically, it was found that the use of postoperative radiation therapy was unnecessary in some patients (35,36). It was also noted that combination chemotherapy, consisting of Vincristine, Dactinomycin, and Doxorubicin was more effective than any one drug used alone. High- and low-risk groups were identified based on the recognition of certain unfavorable pathologic subtypes.

In NWTS-III, which was conducted from 1979 to 1986, attention was focused on reducing the amount of therapy in order to limit complications. Stage 1 patients had a substantial reduction in the amount of chemotherapy while retaining excellent survival. It was noted that stage 2 patients with favorable histology could be treated without radiation therapy. The elimination of Doxorubicin from the chemotherapy routine decreased cardiotoxicity. Higher stage patients did well despite a reduction in radiotherapy, further reducing comorbidity.

NWTS-IV was completed in 1994. Single agent treatment, given in a pulse fashion, was found to provide equivalent survival rates compared to multidrug regimens. The duration of chemotherapy was successfully reduced in patients with favorable histology. It was additionally noted that adding Cyclophosphamide to a multidrug chemotherapy regimen improved the 4-yr relapse-free survival in some cases.

NWTS-V was opened in 1995 and was designed to address several important questions. Given the preponderance of evidence implicating chromosomes 16Q and 1P in the pathology of Wilms' tumor, this study seeks to determine if loss of heterozygosity of these chromosomes is associated with poor prognosis. NWTS-V will analyze the effect of increased DNA content in tumors with otherwise favorable histology. This study also seeks to determine whether subcategories of patients with low-stage, favorable histology tumors can be treated with surgery alone. Patients with diffuse anaplasia and clear cell sarcoma are being treated with a new regimen that includes Otoposide and Cyclophosphamide. Finally, NWTS-V will establish tissue banks to facilitate future molecular biological analysis.

CAUSATION

A genetic etiology for Wilms' tumor was initially inferred because it occurs in association with a variety of other disorders (*see* Table 8). These disorders can be grouped by the presence or absence of overgrowth as an element of the symptom complex. Included among the overgrowth complexes is the Beckwith-Wiedemann syndrome, which consists of various anomalies including macroglossia, nephromegaly, and hepatomegaly associated with limb overgrowth (37). The mode of inheritance is thought to be autosomal dominant and the incidence of cancer, including Wilms', in patients with Beckwith-Wiedemann syndrome may be as high as 20%.

Isolated hemihypertrophy is most commonly manifested as leg overgrowth. This disorder is associated with a 5% incidence of Wilms' tumor (33,38). Other overgrowth syndromes associated with Wilms'

Table 8
Listing of Syndromes Associated with Wilms' Tumor

<i>Syndrome name</i>	<i>Associated findings</i>
Beckwith-Weidemann WAGR	Macroglossia, omphalocele, hemihypertrophy Aniridia, GU abnormalities, mental retardation, Wilms'
Denys-Drash	Genital anomalies, nephritis
Pearlman's	Gigantism, mental retardation
Sotos	Macrocephaly, developmental abnormalities
Individual findings associated with Wilms'	Aniridia, Trisomy, 18, Familial Wilms'

WAGR, Wilms' tumor, aniridia, genital anomalies, and mental retardation syndrome; GU, genitourinary.

tumor include Pearlman syndrome, Soto's syndrome, and Simpson-Golabi-Behmel syndrome (39).

Wilm's tumor has also been associated with complexes that do not involve overgrowth. The Denys-Drash syndrome includes pseudohermaphroditism, mesangial sclerosis, and nephroblastoma (40). This syndrome has been associated with mutations of chromosome 11p13 (41). Aniridia has a well-known association with Wilms' tumor, alone and as an element of the Wilms' tumor, aniridia, genital anomalies, and mental retardation (WAGR) syndrome. Identifying the relationship between Wilms' tumor and other anomalies has allowed researchers to better understand the genetics of the tumor, and clinicians to screen patients who are at risk. Such screening is commonly performed by ultrasound at 4-mo intervals (42,43).

The first genetic anomaly linked to Wilms' tumor was found in patients with the WAGR syndrome (44,45). These patients were shown to have deletions in the p₁₃ segment of chromosome 11. Deletion of this segment was found to be a causal factor in the development of Wilms' tumor. Thus, it was deemed a Wilms' tumor suppressor gene and named *WT1* (46,47). Mutation of *WT1* has also been associated with a variety of other genitourinary anomalies including cryptorchidism and hypospadias. These findings suggest that *WT1* has an important role in the development of various genitourinary organs (48). More recently, a second Wilms' tumor gene, *WT2*, has been identified on the short arm of chromosome 11, 11P15.5 (49). This abnormality is associated with the Beckwith-Wiedemann syndrome. Other cancers also show loss of heterozygosity in the 11P15 region so *WT2* may be important in a variety of different can-

cers (50). Other molecular markers currently being assessed include loss of heterozygosity in chromosomes 16Q and 1P.

PATHOLOGY

Wilms' tumor often presents as a large rounded mass that compresses the adjacent normal renal tissue forming a pseudo capsule. Seven percent of the tumors are multicentric. This multicentricity is considered by some to be a contraindication to treatment by partial nephrectomy.

The classic description of Wilms' tumor is that of a triphasic population of cells including a blastemal component, a stromal component, and an epithelial component. The relative proportions of these cells can vary from tumor to tumor and may only consist of one or two of these components (51). Skeletal muscle, cartilage, and other epithelial types may be found in these tumors.

Unfavorable histologic subtypes have been identified in patients with Wilms' tumor. These include rhabdoid, and sarcomatous types, which are now are considered to be distinct from Wilms' tumor and are referred to as rhabdoid tumor and clear cell sarcoma of the kidney respectively. While representing only 10% of all Wilms' tumors, these subtypes were responsible for half of the deaths associated with Wilms' tumor.

Anaplasia is defined by nuclear enlargement, hyperchromasia, and increased mitotic figures. Tumors with these features have been identified as having abnormalities of *p53* tumor suppressor gene function and tend to be resistant to chemotherapy (52). Anaplastic features can occur either focally or diffusely in a tumor (53). The term *diffuse anaplasia* may refer to the presence of anaplasia in more than one portion of a tumor, or in multiple tumor foci. Diffuse anaplasia has a particularly poor prognosis. Tumor histology is determined to be favorable or unfavorable based on the absence or presence of anaplasia.

Neovascularity is commonly seen in Wilms' tumor. Promoters of neovascularity, such as vascular endothelial growth factor, are present in Wilms' tumor specimens and are regulated by transcriptional proteins such as hypoxia inducible factor (54). Several investigators are exploring antiangiogenic strategies for Wilms' tumor (55).

Nephrogenic rests represent potential precursor lesions of Wilms' tumor. They have been identified in one percent of infant kidneys at postmortem examination and are present in up to 40% of kidneys removed for Wilms' tumor (56). Two types of nephrogenic rests have been identified, perilobular or intralobular, based on their position within the kidney. Because renal growth occurs in a centrifugal fashion, those nephrogenic rests found to be intralobular reflect an earlier developmental event. Hence, patients with intralobular nephrogenic rests

Table 9
Radiologic Differences Between Wilms' Tumor
and Nephrogenic Rests

<i>Wilms' tumor</i>	<i>Nephrogenic rest</i>
Lesion are rounded	Lesions are ovoid
Expand over time	Size remains constant
Originate deep within kidney	Originate superficially
Solitary lesion	Multiple lesions

Adapted from ref. 57a.

develop Wilms' tumor at an earlier age and these tumors are associated with syndromes such as WAGR and Denys-Drash (56). Nephrogenic rests commonly involute and do not develop into Wilms' tumor. However, it has been shown that children with unilateral Wilms' who have nephrogenic rests in the contralateral kidney are at an increased risk for Wilms' tumor in the future (57). Therefore, children identified as having nephrogenic rests should undergo surveillance for Wilms' tumor. Table 9 (57a) lists the radiographic characteristics of nephrogenic rests and compares them to those of Wilms' tumor.

CLINICAL PRESENTATION

The most common clinical presentation of a child with Wilms' is a palpable abdominal mass. Tumors are frequently not identified until they are quite large and may first come to the attention of the caretaker. Infrequently, signs and symptoms such as abdominal pain, hematuria, or constitutional symptoms may present. Hematuria may be present in up to 25% of patients (58). Tumor rupture can present as an acute abdomen. Hypertension may occur in up to 25% of cases and has been attributed to the expression of renin (59). During the physical examination of these patients, attention should be placed on identification of other associated physical abnormalities such as aniridia or hemihypertrophy.

Preoperative Evaluation

The NWTS has developed criteria for initial evaluation of a patient with suspected Wilms' tumor. Laboratory evaluations include a complete blood count, urinalysis, blood chemistry consisting of blood urea nitrogen, creatinine, bilirubin, serum glutamic-pyruvic transaminase, alkaline phosphatase, and albumin. Radiologic examinations are designed to establish the function of the contralateral kidney, evaluate whether or not renal vein or inferior vena cava thrombus is present,

Table 10
Recommendations for Initial Evaluation and Staging
of Patients with Wilms’ Tumor

<ul style="list-style-type: none">• History: to include family history of Wilms’ or other cancer, congenital defects, and benign tumors.• Physical examination: to include evaluation of BP, wgt, hgt, size of liver and spleen, lymph nodes, and associated congenital birth defects.• Laboratory evaluations:<ul style="list-style-type: none">CBC with differentialUrinalysisComplete blood chemistriesBone marrow aspirations (CSK only)• Radiologic evaluations<ul style="list-style-type: none">PA and lateral chesCT of chestAbdominal ultrasoundCT of abdomenSkeletal survey and bone scan (CSK only)MRI brain (CSK and rhabdoid only)

All studies and data should be accrued in accordance with NWTs-V protocol, available on COG website see institutional PI for access to protocols.

and establish whether or not there are metastases. The recommended radiologic evaluations include plain films of the chest and CT of the chest. Abdominal ultrasound is often performed to determine the original site of the tumor but, is also very helpful in evaluating the presence of renal vein or inferior vena cava thrombus. CT of the abdomen is performed and in select patients, X-ray skeletal survey or a radio-nucleotide bone scan is recommended. This is specifically important in patients with clear cell sarcoma of the kidney because of the tendency of the tumor to metastasize to these sites. Additionally, patients in high-risk categories, which include clear cell sarcoma of the kidney and rhabdoid tumor, should have an MRI of the brain because of the propensity of the tumor to present with cerebral metastasis. Table 10 summarizes the preoperative staging of patients with suspected Wilms’ tumor.

TUMOR STAGING

In the United States, the most common staging system is that employed by the NWTs. Stage is based on a surgical classification system. A review of the most recent NWTs study reveals that, of all enrolled patients, 41.8% had stage 1 tumors, 27.5% had stage 2 tumors, 21.5% had stage 3 tumors, and 9.3% had stage 4 tumors (60).

Stage 1 tumors are limited to the kidney and are completely resected. The renal capsule has an intact surface and the tumor was not ruptured or previously biopsied. The vessels of renal sinus are not involved.

Stage 2 tumors extend beyond the kidney but have been completely resected. There can be regional extension of the tumor or extension and invasion into the renal sinus. Blood vessels outside the renal parenchyma, including those of the renal sinus, may contain tumor. The tumor may have been previously biopsied or there may have been frank spillage that was contained to the flank at the time of surgery.

In Stage 3 tumors, residual nonhematologically spread tumor is present and confined to the abdomen. This may represent lymph node involvement, tumor penetration through to the peritoneal surface, tumor implants on the peritoneal surface, or gross or microscopic tumor remaining postoperatively. Included in this group are tumors that cannot be completely resected because of local infiltration. Intra-abdominal spillage is included here.

Stage 4 tumors are those that present with hematogenous metastases to the lung, liver, bone, or brain and include pulmonary nodules not detected on chest radiograph, so-called "CT only metastases," which do not mandate treatment with whole lung irradiation.

Stage 5 tumors have bilateral involvement that is present at the time of diagnosis.

TREATMENT

Table 11 outlines the current treatment protocols as delineated in the NWTS-V. In the NWTS-V studies, patients are treated with an initial surgical resection for appropriate staging unless extenuating circumstances are present.

SURGICAL APPROACH

Currently, the NWTS group continues to advocate a transperitoneal approach for adequate staging at the time of surgery. A transverse upper abdominal incision is typically used. Staging involves evaluation of the liver, regional lymph nodes, and contralateral kidney. Staging of lymph nodes is particularly important as it is a main determinant of future relapse. The current protocol suggests that contralateral surgical exploration is necessary despite improvements in imaging techniques, such as CT and MRI. This is recommended based on the results of NWTS-IV, which found a 7% incidence of bilateral lesions missed by initial radiographic screening studies (61). After completion of NWTS-V, the decision as to whether or not contralateral exploration is performed will

Table 11
Brief Overview of Protocols for the Treatment of Wilms' Tumor

Stage I - Favorable histology	Surgery
Stage I - Focal or diffuse anaplasia	Chemotherapy: Dactinomycin Vincristine
Stage II - Favorable histology	As above
Stage III - Favorable histology	Surgery
Stage II or III - Focal anaplasia	Abdominal radiation Chemotherapy: Dactinomycin Vincristine Doxirubicin
Stage IV - Favorable histology or focal anaplasia	Surgery Abdominal radiation/pulmonary radiation Chemotherapy as for stage III
Stage V	Tumor biopsy Chemotherapy 2nd look laporatomy
State II or IV - Diffuse anaplasia	Surgery Abdominal radiation/pulmonary radiation (if lung mets) Chemotherapy: Vincristine Doxorubicin Etoposide Cyclphosphamide + MESNA

See NWTS for specific regimens and for treatment recommendations for treatment of Clear cell sarcoma of the kidney.

be at the discretion of the surgeon. Many feel that exploration of the contralateral kidney is not necessary as improvement in radiologic studies has made the chance of missing a lesion very small.

After initial assessment for disseminated disease, attention is focused on the tumor. It is approached by reflecting the ipsilateral colon. Handling the tumor with care is important as tumor rupture can result in an upstaging. The surgeon should palpate the renal vasculature to ensure that there is no thrombus even if it has been excluded by radiologic imaging. The “patient is then meticulously dissected from the tumor”. Significant neovasculture can be expected and must be controlled. The ureter is generally taken as far down as convenient and ligated. Care must be taken if intrapelvic extension of the tumor is suspected to avoid tumor spillage.

Surgical morbidity was reviewed in NWTs-IV and an overall incidence of surgical complications in 11% of patients was noted (62,63). The most common complications were hemorrhage and small bowel obstruction.

In special circumstances, alterations in the normal scheme of up-front surgery may occur. Bilateral Wilms' tumor is one of the circumstances in which up-front surgery is contraindicated. The incidence of synchronous bilateral Wilms' tumor is approx 5%. Metachronous lesions occur much less frequently (64,65). The diagnosis of bilateral Wilms' tumor is not an indicator of poor outcome. However, it is important to note that these patients are at increased risk of renal failure. Current recommendations are for initial surgical biopsy of both kidneys. Any suspicious lymph nodes should be biopsied and a surgical stage assigned to each side. Patients with bilateral disease go on to have chemotherapy. Following the completion of chemotherapy, patients with bilateral disease undergo a second look operation and patients having a substantial response to therapy, may then undergo partial nephrectomy. Using this strategy, it has been suggested that preservation of renal parenchyma may be accomplished. It should be noted that if response to chemotherapy is poor delaying surgery may prove deleterious to patient survival. In some cases bilateral nephrectomy may be appropriate.

Another group of patients that may require preoperative chemotherapy are those with inoperable tumors. Tumors may be considered inoperable because of tumor size, extension into the superhepatic portion of the inferior vena cava, or other reasons. Occasionally, a tumor may be considered too difficult to excise based on its massive size. All of these patients may undergo preoperative chemotherapy. Similar to patients with bilateral disease, these patients undergo initial biopsy. After confirmation of the pathologic diagnosis, patients are then stratified into chemotherapy regimen. Patients achieving inadequate response to chemotherapy may then undergo delayed surgical excision. Patients without response may then be considered for additional radiotherapy in an attempt to see if tumor shrinkage permitting nephrectomy can be attained.

Whether or not patients with stage 1 Wilms' tumor could be treated simply with surgical excision without follow-up chemotherapy was recently evaluated by the NWTs group (66). Preliminary data had suggested that such an approach might be reasonable for young patients with stage 1 favorable histology tumors. This approach, however, was suspended when the number of tumor relapses exceeded an allowable limit set by the initial design of the study. At this point in time, chemotherapy is still recommended for all patients with stage 1 disease.

Recently, the role of partial nephrectomy for unilateral tumors has been considered. The interest in this has been driven primarily by the success of renal preservation in patients with bilateral Wilms' tumors. As the majority of tumors are too large at initial presentation for partial nephrectomy, little experience has been had by the NWTs group with this question. However, our colleagues in the SIOP study have found that preoperative chemotherapy can reduce a tumor burden and make partial nephrectomy possible. When evaluating a population of patients with bilateral Wilms' tumor undergoing partial nephrectomy it was found that the incidence of local recurrence has been 7.5% (67).

The primary impetus for this approach has been concern over long-term renal function. However, recent study by the NWTs group has shown that the chance of developing renal failure after treatment for unilateral Wilms' tumor appears to be very low (62). Therefore, the current recommendation is that partial nephrectomy be used only for patients with bilateral Wilms' tumor, solitary kidney or pre-existing renal insufficiency. An additional consideration may be patients with genetic diseases that predispose them to recurrence of Wilms' tumor.

ROLE OF PREOPERATIVE CHEMOTHERAPY

The SIOP group has advocated the use of preoperative chemotherapy since the 1970s. It is this group's belief that this approach results in tumor shrinkage and reduces the risk of intraoperative complications such as tumor rupture or spillage (68). Neoadjuvant therapy may also decrease the risk of micrometastasis and produce downstaging of the tumor.

Although this group has had excellent success in treating patients with preoperative chemotherapy and their survival statistics are similar to those presented by the NWTs group, the current argument is that staging following chemotherapy may not give an adequate assessment of the original tumor burden or stage. Therefore, classifications of patients into high or low risk may not be accurate.

OUTCOMES

Survival of Wilms' tumor patients has increased dramatically from the time of discovery of this tumor. Table 12 presents survival results from randomized patients enrolled in the NWTs-III study. As is evident, patients with favorable disease of stage 3 or lower, enjoy overall survival rate roughly in excess of 90%. However, patients with unfavorable disease do not enjoy such high survival.

Table 12
Published Survival Statistics
from NWTs III

Stage I FH	96%
Stage II FH	92%
Stage III FH	91%
Stage IV FH	81%
Stage II-IV diffuse anaplasia	55%

Data derived from NWTs IV represents relapse free survival.

Patients who survive Wilms’ tumor and have been disease-free for more than 5 yr are enrolled in the long-term survival and late effects study of the NWTs group. Analysis of these patients showed that patients had musculoskeletal problems such as scoliosis much more frequently if they had received radiation (69). Damage to the reproductive system, both male and female, has also been documented as a result of radiation therapy (70,71). Systemic effects such as congestive heart failure associated with anthracycline has been documented in roughly 4% of patients (72). And, finally, children treated for Wilms’ tumor are also noted to be at increased risk for secondary malignant neoplasms (73).

FUTURE DIRECTIONS

Recently, interest has been focused on analyzing chromosomal abnormalities in patients with Wilms’ tumor in the belief that they may allow more appropriate stratification into risk groups. Specifically, recent investigations have explored the roles of chromosomal abnormalities on chromosome 16q, 1p, and 1q. The second most common site of loss of heterozygosity in Wilms’ tumor is a long-arm chromosome 16. On this chromosome at location 16q22 lies the *CTCF* gene (74). This gene encodes a protein that binds to DNA and is responsible for maintaining normal imprinting of the insulin-like growth factor 2 gene (*IGF2*). It is believed that a loss of heterozygosity of this gene might predispose to methylation and altered function of the *IGF2* gene. Currently, investigators are evaluating whether or not alterations in chromosome 16q could play a role in Wilms’.

Recently, the UKs Children’s Cancer Study Group reported their findings of an analysis of chromosome 1q expression in 18 cases of Wilms’ tumor with favorable histology (75). This interesting study demonstrated that relative overexpression of long-arm chromosome 1

was present in all tumors that subsequently went on to relapse. These findings are significant and if confirmed may allow for screening of the 1q region in order to stratify patients into high- and low-risk groups.

Although overexpression of several genes such as *BCL2*, *WT1*, and *Survivin* have been associated with recurrence, substantial information remains to be obtained regarding the specific genes involved in Wilms' tumors progression and outcome. New technologies such as microarray analysis may allow the identification of other genes responsible involved in Wilm's tumorigenesis (76).

NEUROBLASTOMA

Neuroblastoma (NB) is the most common solid tumor of childhood. It is known to arise from the cells of the neural crest that form the adrenal medulla and the sympathetic ganglion. Tumors of this origin include neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. The former two are remarkable because of their potential for spontaneous regression, in children of less than one year of age.

Insight into this disease has been vastly increased by our expanding knowledge of the molecular biology of this tumor and by epidemiologic studies. Specifically, research has shown the importance of *N-MYC* (*MYCN*) overexpression and chromosomal abnormalities in the pathogenesis and prognosis of this tumor (77). On the clinical front, two major studies have demonstrated that tumors in newborn children are substantially different from those that occur at a later age. As a consequence, it is now known that tumors in newborns have a much greater potential for spontaneous regression (78). Sadly, we have yet to see this expansion of our understanding result in a direct benefit in terms of patient survival. The outcome for patients with disseminated NB is still generally poor, and as a whole, survival of this disease does not enjoy the improvement that has been seen in other pediatric tumors.

Population-based studies indicate that the annual incidence of NB in North America is roughly 10 to 11 per 1 million children under the age of 15. At diagnosis, more than 50% of NBs are associated with advanced disease (stages 3 or 4) and, overall, 40% of patients have disseminated disease at diagnosis. Ten-year survival rates for patients with stage 3 and 4 disease are 63% and 21%, respectively. There is no racial or geographic predominance; however, familial association has been noted (79).

CAUSATION

No environmental or chemical carcinogens have been associated with NB. NBs can occur in patients with inheritable mutations (80). As many

as 20% of NBs can be related to inheritable chromosomal abnormalities. Familial cases have been reported and there is a suggestion of an autosomal dominant pattern of inheritance. In these familial cases, a significant percentage of patients may have bilateral or multifocal tumors. The risk of a sibling or an offspring of a patient with NB having NB, is less than 6% (81).

There are various chromosomal abnormalities that have been identified in patients with neuroblastoma. The protooncogene, and *MYCN* has been shown to have a strong association with NB (82,83). Specifically, *MYCN* amplification has been associated with high-grade advanced disease and poor prognosis (84). We know today that *MYCN* gene amplification is seen in approx 40% of patients with advanced NB and less than 10% of those with lower stage disease. Obviously, however, *MYCN* expression does not explain progression in all cases of neuroblastoma. More recently, deletions of chromosome 1 and gains in chromosome 17 have been shown to be important determinants of outcomes in patients with neuroblastoma. Specifically, gains in chromosome 17Q with concomitant deletions in chromosome 1P have been shown to be an adverse prognostic factor (85). Patients with 17Q gain had only a 30% survival at 5 yr as compared to patients without a 17Q gain who enjoy an 86% 5-yr survival (85).

Other factors shown to be associated with NB outcome may also play a role in causation. Neuropeptide receptors such as nerve growth factor, brain-derived neurotrophic factor and neurotrophin-3 and their associated receptors, TRK-A, TRK-B, and TRK-C, are examples. Specifically, *TRK-A* gene expression has been associated with lower incidence *MYCN* amplification, lower stage, and more favorable outcomes (86). Less is known about TRK-B and TRK-C but it appears that some relationship may exist between patient outcome and expression of these receptors for neurotrophic factors.

PATHOLOGY

The gross appearance of NB is that of a nodular, highly vascular, purple to whitish mass of varying size. There are frequently areas of hemorrhage, necrosis, and calcification associated with the tumor. NBs have been classically identified by the formation of nuclei into pseudorosettes. This classic histologic pattern, however, is only present in about 50% of cases (87). Nuclei may vary in size and nuclear chromatin may be present. Ganglioneuroblastomas and ganglioneuromas represent evidence of maturation within the tumor. In poorly differen-

Table 13
Shimada Classification System

	<i>Favorable histology</i>	<i>Unfavorable histology</i>
Stroma rich	Well differentiated or admixed	Nodular
Stroma poor: <1.5 yrs	MKI <200/5000	MKI >200/5000
1.5–5 yrs	MKI <100/5000 differentiated	MKI >100/5000 undifferentiated
>5 yrs		All

MKI, mitotic/karyorrehectic index.

tiated tumors, which may be difficult to identify, neuron-specific eno-
lase staining is useful (88).

Shimada’s Classification

In 1984, Shimada and colleagues published a widely accepted age-
linked classification system based on the morphology of the primary
tumor (*see* Table 13) (89). This classification system has proved useful
in predicting outcome. Shimada’s classification system divides tumors
into two categories: stroma poor and stroma rich. Stroma-rich tumors
are then further subdivided into favorable and unfavorable histology.
Patients with stroma-rich tumors and unfavorable histology (nodular
tumors) have an extremely poor long-term survival (18%). The stroma-
poor tumors, on the other hand, are also divided into favorable and
unfavorable groups based on patient’s age, evidence of maturation, and
a mitosis-karyorhexis index. Patients with unfavorable category,
stroma-poor tumor have a very poor long-term survival (less than 10%).

Joshi Classification

In 1992, Joshi and co-workers published a new classification sys-
tem for NBs, which was also age-linked and based on histology of the
tumor (*see* Tables 14 and 15) (79). Similarly, this system divides
patients into two risk groups. The primary advantages of this system
appears to be consistency between examiners, however, this has not
been confirmed. Further studies revealed that this system also corre-
lated with other nonhistologic factors such as the DNA index or *MYCN*
oncogene levels. Future investigators will evaluate the utility of both
these classification systems.

Table 14
Joshi Histologic Classification System

<i>Tumor grade</i>	<i>Mitotic rate</i>	<i>Calcification</i>
1	Low	Yes
2	Low or	→ Yes
3	High	

Low mitotic rate is defined as 10 or fewer after evaluation of 10 hpf.

See Table 15 for assignment based on grade.

Table 15
Joshi Risk Groups Based on Histology

	<i>Grade 1</i>	<i>Grade 2</i>	<i>Grade 3</i>
Low risk	All	≤1 yr	None
High risk	None	>1 yr	All

Ganglioneuroma vs Neuroblastoma

Ganglioneuroma is a benign tumor that exists as part of the spectrum of tumors derived from the neural crest. In distinction from NBs, most ganglioneuromas occur in older children and are located in the posterior mediastinum and the retroperitoneum (90). These tumors may secrete catecholamines and may grow to quite a large size before impingement on vital structures prompts diagnosis (91). Grossly, these tumors have a very firm capsule and can be rubbery in consistency. Microscopically, they are characterized by mature ganglion cells, which are scattered throughout a mixture of Schwann cell matrix (58). The origin of this tumor is unclear. They may, in fact, result from a maturation of a ganglioneuroblastoma or an NB. They infrequently metastasize. Differentiation between ganglioneuroblastoma and NBs is much more difficult. In Shimada’s classification, ganglioneuroblastomas are generally well differentiated and rich in stroma. These tumors are associated with a very good long-term prognosis.

PRESENTATION AND EVALUATION

Presentation of NB can vary significantly based on the initial site of the tumor and the presence of metastases. For the purposes of this chapter, we confine the discussion to NBs that occur in the abdominal cavity or in the pelvis. An abdominal mass is the most common presenting

complaint in these patients reported in 50–70% of cases (79). NBs arising primarily in the pelvis are uncommon.

An abdominal mass, abdominal pain, or emesis may be indicative of NB. Typically, the abdominal mass has been described as hard and irregular, and classically, has been described as extending across the midline, in contradistinction from Wilms' tumors, which are thought to typically not cross the midline. Thoracic tumors may present with respiratory distress or dysphagia. Spinal cord compression by a paraspinal tumor may cause presentation with neurologic symptoms. Patients with pelvic NB may present with difficulty in urination or complaints related to defecation. Lesions of the brain can produce Horner syndrome as well as other changes such as heterochromia of the iris and enophthalmos. Finally, because more than 90% of NBs produce vasoactive substances, patients may present with systemic symptoms like, diarrhea, weight loss, flushing, palpitations, and hypertension.

Neuroblastoma Screening

Secretion of catecholamines by NB has allowed for mass screening programs to be evaluated in Japan and Canada. Specifically, detection of urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA) may allow for early diagnosis. Sensitivity for these techniques has been reported to be up to 96% (92).

In these countries, mass screening has detected the existence of two different types of NBs—those with good prognosis, which are anaploid, have no *MYCN* amplification, secrete catecholamines, and can be detected early vs those NBs, which are diploid, have *MYCN* amplification, do not secrete catecholamines early, and are more difficult to detect by screening. It was thought that by early screening the outcomes of patients with NB might be able to be improved (93). However, it appears that studies of this nature have been faulted by selection bias, and the more favorable outcomes noted in these studies may be due to the fact that more NBs that would have regressed on their own have been detected. Currently, the belief is that early screening does not produce a more favorable outcome.

Laboratory Evaluation and Tumor Markers

Patients with NB should have a complete blood count. Anemia can be a consequence of systemic disease associated with widespread bone metastasis. A full set of coagulation studies should also be obtained as patients with liver metastasis may have alterations. Electrolytes should also be evaluated. All patients suspected of NB should have a bone marrow aspiration as a high percentage of these patients will have

bone marrow involvement despite the absence of metastatic tumor on skeletal survey.

As 90% of NBs secrete one of the two metabolites of catecholamines, urinary collection for catecholamines should be performed. Specifically, collection for VMA and HVA should be obtained in 24-h urine collections (94). Urinary levels of VMA and HVA can also be monitored during therapy as a reduction is noted in the majority of patients responding to therapy (95).

Lactate dehydrogenase (LDH) is also monitored in patients with NB. High serum levels of LDH represent a high proliferative activity within the tumor and it has been shown that serum LDH levels elevated greater than 1500 IU/l have been associated with poor prognosis (96). Serum ferritin should also be evaluated in patients as it has been shown that serum ferritin levels greater than 150 ng/ml are often seen in advanced cases of NB (97). Both these levels and LDH levels should trend downward if treatment is effective.

More recently, it has been identified that NBs ubiquitously express the ganglioside GD2. This ganglioside can be detected in the plasma of patients with NB and a decrease of circulating tumor-derived ganglioside GD2 has been noted in response to successful therapy of patients with NB (98). Additionally, more recent studies by Lo Piccolo et al. have shown that GD2 synthase, which is a key enzyme in the production of the ganglioside GD2, may be also another valuable tumor marker for the detection of rare NB tumor cells (98a). Finally, the ability to detect single NB cells found in the peripheral blood has been recently documented (99). Using highly sensitive reverse transcriptase polymerase chain reaction (RT-PCR), an assay has been developed that will allow detection of a single NB cell in 10^7 cells of peripheral blood. This type of analysis may become useful in following patient relapse in the future.

Imaging Studies

Ultrasound is often the initial modality for evaluation of an abdominal mass and can delineate major vessels and organs that may be involved with the tumor. Color doppler can supply information regarding whether the vasculature is involved with tumor. However, at this point in time, CT and MRI are the primary modalities used to image patients and assess the extent of disease. CT scan demonstrates calcification in more than 80% of NBs (100). Intraspinal extension of the tumor can also be determined by enhanced contrast CT as well as MRI. MRI may also be particularly helpful in looking for vascular involvement and central nervous system involvement. Recently, it has been suggested that MRI is the best imaging modality for the diagnosis and staging of

NB (101). Additionally, MRI may also be able to detect bone marrow metastasis and its sensitivity and accuracy allow for sequential evaluation of disease during treatment.

Metaiodobenzylguanidine Imaging

Metaiodobenzylguanidine imaging (MIBG) is used for scintigraphic imaging of NB. MIBG is stored within granules in chromaffin cells, which are present in NB. Studies have shown that the MIBG scan is the imaging study of choice for evaluation of bone and bone marrow in patients with NB (102). Reported sensitivities for MIBG for the detection of NB with metastatic lesions are 82% and 91%, for bone and bone marrow, respectively. MIBG scan can also be used to monitor response to therapy.

Bone marrow biopsy has been a standard of care for the detection of bone marrow involvement in patients with NB. Aspiration is a common technique employed and specific antibody stains such as antiganglioside GD2, neuron-specific enolase, and ferritin are used in order to identify NB cells within the bone marrow (103). There has been a suggestion that over time, bone marrow aspiration may be replaced by MIBG scanning (104). However, this awaits further evaluation.

Tumor Staging

Previously, multiple staging systems were used for NB. These included the Evans classification and the staging system advocated by the Pediatric Oncology Group. More recently, these have been supplanted by the International Neuroblastoma Staging System (INSS) (105). This staging system attempts to incorporate features of the other commonly used staging systems into one practicable system and is shown in Table 16.

TREATMENT

Treatment of patients with NB is based on risk-group analysis as derived from their INSS stage and from other identified biologic markers. Patients are grouped into low-, intermediate-, and high-risk groups in this fashion.

For patients with low-risk disease, stages 1, 2, and 4S, outcomes are typically very good. Stage 1 patients can generally be treated with surgical excision alone and enjoy an overall disease-free survival of approximately 89% (106). Patients with stage 2 tumors may require adjunctive treatment with radiotherapy or chemotherapy; however, they similarly enjoy an excellent survival. A report of 156 patients with stage

Table 16
International Neuroblastoma Staging System

Stage 1	Localized tumor completely resected Ipsilateral nodes negative
Stage 2a	Localized tumor incompletely resected Ipsilateral nodes negative
Stage 2b	Localized tumor incompletely resected Ipsilateral nodes positive Contralateral nodes positive
Stage 3	Unresectable unilateral tumor crossing midline ± Regional nodes Unilateral tumor with contralateral nodes Midline infiltrating tumor (nodes or primary tumor)
Stage 4	Primary tumor with dissemination
Stage 5	Localized primart tumor with limited dissemination to skin, liver and or bone limited to infants < 1 yr of age

2 NB found 90% 6-yr disease-free survival whether or not adjunctive measures were used (107). In stage 4S tumors, resection of the primary tumor is controversial. In this group, it appears that molecular biologic markers have a great impact on whether a benign course or a more aggressive course is followed.

Intermediate-risk patients are considered patients with INSS stage 3 or 4 tumor without additional biologic risk factors. Specifically, these patients should lack *MYCN* amplification, have near diploid or tetraploid tumors, a low TRK expression, and do not have 17Q/1P translocation. These patients also tend to be older than 1 yr of age. In this category, treatment usually consists of aggressive multimodal chemotherapy and irradiation to metastatic sites.

High-risk patients comprise INSS stages 3 and 4 with adverse biological markers. These patients require an aggressive approach with multimodal therapy involving chemotherapy, radiotherapy, and surgery. Despite this approach, many of these patients have an unfavorable prognosis. Survival for this group of patients remains very low, in the 15–35% range (108).

FUTURE DIRECTIONS

As a consequence of the poor outcome for patients with advanced disease, intense efforts have been focused on developing new therapeutic

tic strategies for NB. Differentiating agents have been used with some success in a variety of tumors. In vitro studies demonstrated that treatment of human NB cell lines with all-*trans*-retinoic acid (RA) resulted in diminished *MYCN* RNA expression and arrested cell proliferation (109). This effect appears to be mediated by RA receptors that are present in a large number of NB cells. Based on these in vitro results and anecdotal reports of success in using 13-*cis*-RA in the clinical setting, investigators began designing larger clinical trials using differentiating agents. The Children's Cancer Group (CCG) undertook a phase 1 trial (CCG-3891) to evaluate 13-*cis*-RA in high-risk NB. On final analysis of CCG-3891 it appeared that 3-yr event-free survival (EFS) was higher for patients receiving RA. Patients undergoing bone marrow transplant (BMT) plus RA had a 3-yr EFS of 55% vs 41% for those undergoing BMT alone. Similarly, patients undergoing chemotherapy plus RA fared better (33% EFS) when compared to those undergoing chemotherapy alone, 19% (109). Currently, future trials of RA and synthetic retinoids such as Fenretinide are in development.

The observation that NB has a fairly high rate of regression in infancy has prompted much interest in both apoptotic and or differentiation mechanisms. Much attention has recently been focused on the caspase-8 gene (*CASP-8*) which is a key regulator of the apoptotic cascade. One theory has proported that this potential anti-oncogene undergoes methylation inactivation in *MYCN*-amplified tumors promoting tumor development (110). Other studies have linked *CASP-8* expression and methylation to other neural crest tumors including RMS, medulloblastoma, retinoblastoma, and neuroendocrine-derived lung tumors. Although its true impact remains unproven, several investigators are currently evaluating this pathway in NB.

Investigators continue to explore the role of anti-angiogenic strategies in NB. Initial work using strategies such as anti-VEGF antibodies that produced by modest results in animals has given way to new strategies. Spurbeck et al. recently reported their work utilizing retroviral-mediated delivery of a matrix metalloproteinase (MMP) inhibitor (TIMP-3) to evaluate its effect on tumor growth in severe combined immunodeficiency mice (111). Their study showed that inhibition of matrix metalloproteinase, which are responsible for the extracellular matrix remodeling associated with angiogenesis, substantially diminished angiogenesis and tumor growth. More recently, a pro-angiogenic role for *MYCN* amplification has been postulated. Utilizing a chick embryo chorioallantoic membrane assay, Ribatti et al. suggested a role for *MYCN* amplification in tumor-associated angiogenesis (112).

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Pediatric Urology

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The practice and science of pediatric urology has changed rapidly in the last few years with the availability of new surgical techniques, more informative prenatal evaluations, and better biomedical substances. In *Pediatric Urology*, leading pediatric urologists from major academic institutions offer a unique practice-oriented approach to these new developments. Here, the practicing urologist will find informative, easy-to-read reviews of the modern evaluation of prenatal hydronephrosis, the standard treatment of reflux vs the newer injectable techniques, and the spectrum of hypospadias treatment along with new developments in bladder exstrophy. Additional updated topics include what's new in undescended testis, the evaluation of difficult duplication anomalies, voiding dysfunction and neurogenic bladders, pediatric stone disease, and the developmental problems associated with genitourinary defects.

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