

III. Other Pediatric Urinary Conditions

15. Pediatric Genitourinary Tumors

Summary

Treatment of renal, bladder/prostate, and testicular tumors in children may entail significant short- and long-term morbidity, as well as the threat of death from metastatic disease or complications of treatment. The large multicenter groups under the umbrella of the Children's Oncology Group (COG) have defined the standard management of these tumors in the United States, and COG continues to develop large prospective studies. We suggest research priorities—studies of the cytogenetic changes underlying tumorigenesis, the evaluation of organ-sparing approaches, and longitudinal study of late effects of treatment on organ function and secondary malignancy risk—which are not currently a focus of COG.

Current Clinical Management

Kidney

The initial treatment for children with kidney cancer (Wilms' tumor is the most common kidney and genitourinary tumor in children) is removal of the affected kidney. Based on the type of kidney cancer and extent of the disease, children receive multiagent chemotherapy with or without radiation therapy. The cure rate for most patients following these protocols is approximately 90 percent.

Bladder

Current therapy for bladder and prostate cancers, which account for 3 percent of pediatric genitourinary tumors, emphasizes bladder salvage.

Most tumors are biopsied and then treated with chemotherapy in the hope of gaining enough tumor shrinkage to allow for bladder preservation. Many children receive pre- and postoperative radiotherapy as well. Survival is approximately 85 percent with this approach, although 40 percent will have lost bladder function after 4 years.

Testis

Yolk sac tumor of the testis is highly curable; prospective multicenter trials in Europe and the United States have shown that a nearly 100 percent survival can be achieved for prepubertal children. However, this cure rate requires removal of the affected testicle and, for patients with metastatic disease, multiagent chemotherapy. Adolescents with mixed germ cell tumors have been managed largely as adults with some combination of removal of the testicle, removal of abdominal lymph nodes, and chemotherapy depending on the stage and histology of the tumor.

Health Impact

Wilms' tumor, cancer of the bladder and prostate (rhabdomyosarcoma), and testicular tumors (yolk sac and mixed germ cell tumors) account for a significant fraction of all solid pediatric tumors. While the outcome for children with genitourinary cancers has improved in the last century, many children still die from these tumors. The children who survive are subject to the long-term complications of chemotherapy, radiation, and surgical removal of some or all of the affected organ.

Research Priorities

Many clinical questions regarding the standard management of pediatric genitourinary tumors are

being addressed by COG. However, these studies are inherently conservative and can answer only a limited number of questions with each protocol. There are many important questions that need to be addressed by additional studies.

Since children treated for genitourinary cancer have a known increased risk for other cancers later in life, clinical studies are needed to identify the specific risk of late secondary malignancies and the implications for initial treatment and long-term surveillance. These should take into account both treatment effect and genetic predisposition to help understand the pathogenesis of the secondary tumors. Other functional endpoints must be evaluated for a variety of pediatric genitourinary tumors: long-term gonadal function in adults treated for testicular tumors in childhood, long-term kidney function in those treated for Wilms' tumor with chemotherapy and radiation, and long-term bladder function after radiation treatment of rhabdomyosarcoma.

Organ-sparing approaches for pediatric genitourinary tumors need to be assessed in terms of safety and effectiveness. For example, in the treatment of Wilms' tumor, partial removal of the kidney has proven effective in special cases; investigation of the wider use of kidney-sparing surgery could significantly reduce the long-term risk to kidney function in these children.

Basic Research

- Elucidate the role of the fetal tissue lesion nephrogenic rests in development of cancer in Wilms tumor patients.
- Apply cytogenetic approaches that identify the genetic and mechanistic basis of genitourinary tumorigenesis as a prelude to intelligent stratification of patients for treatment.

Translational and Clinical Research

- Conduct multicenter studies of organ-sparing approaches for pediatric genitourinary cancers, particularly partial kidney removal for Wilms' tumor.
- Conduct prospective studies of treatment options for adolescents with testicular cancer.
- Evaluate with epidemiologic and outcome studies whether the adult protocols for surgery and chemotherapy used to treat adolescents with testicular cancer including mixed germ cell tumors are appropriate.
- Conduct longitudinal studies of long-term outcomes including renal, bladder, and gonadal function, and the risk of secondary malignancies.
- Conduct phase I/II trials needed to develop new therapies, particularly for patients with high-risk disease.

Infrastructural Needs

- Training of academic urologists capable of undertaking large, prospective clinical trials assessing the evaluation and management of children with pediatric genitourinary cancer.
- Establishment of a pediatric genitourinary cancer patient registry.
- Expansion of the COG tissue banks, with access to non-COG scientists for appropriate studies.
- Administrative mechanisms to encourage multidisciplinary and multicenter collaborative studies.
- Establishment of research awards for the investigation of genitourinary cancers in children.

16. Pediatric Genitourinary Trauma

Summary

The treatment of pediatric genitourinary trauma would greatly benefit from the re-establishment of a national database to track trends in causes and management. Two important questions to be addressed would be the long-term sequelae of major kidney injuries and the value of prompt expert intervention in pediatric genitourinary trauma. Continued research into the basis of graft survival and approaches to combating infection in reconstructive surgery is called for if the results of reconstructive surgery are to be improved.

While trauma centers have increased survival and decreased morbidity, trauma remains the leading cause of death and injury for people between the ages of 1 and 44 years. Both upper urinary tract and genital trauma often occur with other injuries—sports and recreational injuries comprise the largest single reason for primary care office visits outside of routine checkups, and pose unique concerns about future maturation and fertility. Representing 8 to 10 percent of all trauma cases, renal trauma is the most common urological trauma. Most genital trauma is blunt trauma resulting from accidents and falls, and infrequently can have profound psychosocial consequences including incontinence, loss of sexual and reproductive function, and altered body image. Except for a few differences, the evaluation and treatment of pediatric genital trauma parallels that of adults. In general, management is improved by prompt expert intervention. Below, we list some categories of trauma and make recommendations for future research.

Kidney and Ureteral Trauma

Motor vehicle accidents and falls cause most pediatric renal and ureteral trauma. Children

are especially at risk because the rib cage and abdominal musculature is less rigid and well developed than in adults. Most kidneys can be saved, and advances in imaging and resuscitation and support make conservative therapy effective in 85 to 90 percent of cases.

Bladder and Urethral Trauma

These are usually due to falls and accidents; often the pelvis may have been broken. When trauma is suspected, careful, thorough imaging is called for. Management is usually conservative with diversion of the urine and secondary repair after the other injuries have been stabilized.

Penile Trauma

Minor penile injuries usually heal well with little consequence. More serious injuries result from amputation, bites, and surgical mishaps. Bites, especially human ones, pose a high risk of infection and require aggressive treatment with antibiotics and debridement. In circumcision, the glans, if not carefully protected, can be cut or amputated. Current practice is to preserve as much tissue as possible and attempt primary repair. Partial or complete amputations can be reattached. When the amputated segment is unusable, later reconstruction is possible using a penile prosthesis and grafts.

Scrotal and Testicle Trauma

Blunt scrotal and testicle trauma, typically presenting with bruising, swelling, and pain, is common in boys. Severe testicular injuries are rare, comprising fewer than 5 percent of recreation- and sports-related pediatric injuries. Most severe are testicular rupture and traumatic torsion.

Genital Skin Avulsion

Rapid deceleration injury can result in genital avulsion; the loose genital skin can become snagged while the rest of the body continues moving rapidly.

The scrotum, labia, and penile shaft are well vascularized, and unless there is massive infection or tissue loss, primary repair can yield good results.

Perineal Laceration

The perineum can become torn apart as the result of a crush or rollover injury: the pelvic bone splinters, the floor of the pelvis tears, and the urethra and genitalia become disrupted. Management is complex and requires immediate control of bleeding, colostomy to divert the fecal stream, and bony fixation.

Burns

Thermal and electrical burns to the genitalia in children are managed like those in adults. Radiation burns can occur as a side effect of radiotherapy. Treatment requires complete excision of the affected skin and graft reconstruction.

Sex Abuse

Sexual abuse occurs in both boys and girls. It is often underreported because of fear and embarrassment by the child, and overlooked by health care and child care providers.

Research

Pediatric trauma occurs sporadically and it is difficult to make any significant observations without a larger pool of data. Therefore, it needs to be tracked nationally. The National Pediatric Trauma Registry (NPTR) served this purpose for many years. For example, it gave firm evidence on the safety of sports participation for boys with only one testicle or kidney. Unfortunately, it is no longer funded and became inactive in 2003.

Many of the posttraumatic reconstructive surgical techniques require mobilization of healthy tissues for graft coverage and reconstruction. Critical to the improvement of these is a better characterization of the fine vascular and neurological anatomy of the genitalia, as well as improved means of combating infection, which remains the primary complication that jeopardizes reconstruction efforts. For patients with insufficient local skin, research should be directed to better understanding of the use of other tissues, such as the buccal mucosa, and to developing practical engineered tissues grown from donor cells taken from the patient's own genitalia.

Priorities

- Develop new techniques to prolong graft survival and improve functional and cosmetic results.
- Develop improved methods of combating infection as a complication of reconstructive surgery—in ways that deter development of antibiotic resistance.
- Investigate the fine vascular and neurological anatomy of the genitalia.
- Explore the use of other tissues, such as the buccal mucosa, in genital reconstructive surgery and develop practical engineered tissues grown from donor cells taken from the patient's own genitalia.
- Evaluate the effect of prompt intervention at specialty centers.

Infrastructural Needs

A national patient registry and database should be restarted to track trends in the causes and management of pediatric urinary genital trauma.

17. Testicular Torsion

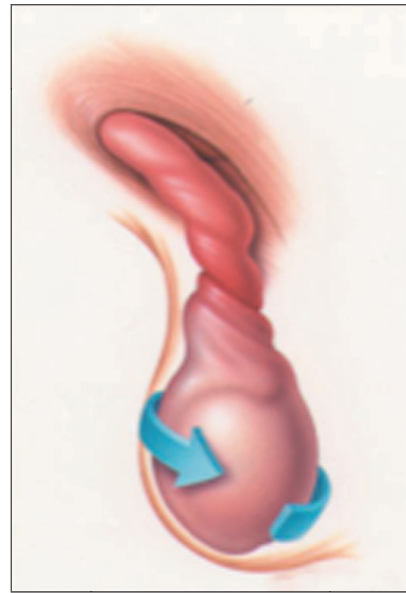
Summary

A delay in the diagnosis and treatment of testicular torsion (spontaneous rotation of the testicle) can result in significant morbidity, including loss of the testicle. While early diagnosis and rapid surgical detorsion is imperative, it is currently difficult to distinguish testicular torsion from other diseases of the scrotum, and new diagnostic approaches are needed. If new therapeutic approaches are to be developed, investigation, at the cellular level, of the consequences of torsion and accompanying ischemia will be essential. New assays are needed to determine testicular viability at the time of surgery.

Testicular torsion is the spontaneous rotation of the testicle, resulting in its compromise or death due to the twisting of the arteries and veins that vascularize it. In humans, the long-term effects of testicular torsion are not well characterized; in animal models, severely reduced testicular blood flow for one hour can lead to permanent testicular atrophy. The degree of hormonal dysfunction in the torsed testis has been variably reported, but there is a consensus that the endocrine function of the testis is significantly reduced acutely after torsion repair.

Health Impact

Affecting one in 4,000 males under the age of 25, testicular torsion is a significant source of emergency room and emergency surgery costs. Delay of diagnosis can result in significant morbidity, including loss of the testicle and medical-legal costs. Fortunately rare, bilateral testicular torsion, which typically presents at birth, results in loss of the testes, sterility, and the inability to produce testosterone.



Testicular torsion (torsion of the spermatic cord) © Todd Buck, Illustration Inc.

Clinical Presentation and Management

Testicular torsion is the most common cause of acute pain with scrotal swelling in children. It is primarily seen in the newborn or in the peripubertal male, and while it is a sporadic disease, several reports of familial torsion, both neonatal and peripubertal, exist in the literature, suggesting a genetic predisposition in some cases. Abnormal attachments between the testis, *vas deferens*, epididymis, vessels and the scrotum, called the “bell-clapper deformity,” have been noted in affected children (autopsy series found 12 percent of testes with this deformity), but currently the molecular and developmental basis of these anomalies is unknown. Occurrence of torsion on one side is associated with increased risk of torsion of the opposite testis. Although testis growth during puberty and trauma have been suggested to trigger the torsion event, this hypothesis has not been proven and should be researched further. Some families and children affected by testicular torsion suffer from worries about future fertility and the absence of one testicle, and occasionally they opt for the placement of a testicular prosthesis.

Diagnosis

Because of the high morbidity associated with this condition, early recognition and rapid surgical detorsion are imperative. However, the clinical and radiological evaluation can be quite challenging, since many other nonsurgical diseases of the scrotum can masquerade as testicular torsion. The diagnosis is made currently by history, physical examination, urinalysis, and ultrasound or nuclear scan. None are perfect, and research addressing alternative strategies for diagnosis is greatly needed.

Therapy

If the diagnosis can be made within 6 hours of the onset of testicular pain, there is a chance that the testis can be salvaged if the torsion is released. However, testicular torsion is of variable severity—dependent upon the duration and degree of twist and therefore the duration and degree of vascular compromise—and there is variability in the severity of symptoms. At the time of surgery, it can be an equivocal and rather subjective decision as to whether the testis is viable, and methods to objectively assess the viability need to be developed. If treated rapidly, the testis can be untwisted, and permanent immobilizing stitches are then placed in both the untorted testis (orchiopexy or septopexy).

Unfortunately, treatment is often delayed and the necrotic testis must be removed (orchiectomy). The opposite testicle is also at risk of torsion, therefore, a simultaneous orchiopexy is performed on the opposite testicle. The worst scenario is that of bilateral testicular torsion, which typically presents at birth. In these fortunately rare cases, virtually none of the testes are salvaged, leaving the child unable to produce testosterone and without reproductive potential.

Priorities for Research

It is important to understand the cellular pathophysiology of testicular torsion so that

new therapies can be developed to deactivate the degenerative cascade initiated by the torsion event. Animal models of testicular torsion have been particularly helpful in understanding the mechanism of torsion-induced damage. There are experimental data to suggest that anti-sperm antibodies might develop after testicular torsion and impair fertility. This has not been definitely proven in humans and should be studied further.

- Characterize at the molecular and cellular level ischemia/reperfusion injury, including subsequent germ cell apoptosis in the torsed testes.
- Improve and validate novel, noninvasive means to detect torsion, such as biomarkers or imaging techniques.
- Identify assays to determine testicular viability at the time of surgery.
- Create medical therapies to diminish ischemia-reperfusion damage to the torsed testis.
- Identify risk factors for torsion; improve its anatomical characterization.
- Define and validate the diagnosis of intermittent torsion by novel biomarkers.
- Assess long-term endocrine function and fertility in patients with past torsion.

18. Phimosis and Circumcision Practice

Summary

The benefits of routine circumcision remain controversial. We suggest that the effect of neonatal circumcision on UTI frequency be evaluated prospectively using cohort-matched groups in a statistically sound longitudinal study.

The foreskin covers the glans or head of the penis. At birth, it is not retractable, but in most children it becomes so by age 5. In some children, formation of a tight ring of scar (phimosis) due to repeat infection, irritation, or tearing prevents retraction; this causes spraying of the urine and traps urine beneath the foreskin, fostering infection in the urine or in the penis. Other health effects of circumcision are somewhat controversial. The tougher and easier to clean exposed glans may increase resistance to STDs, including HIV, and prevents penile cancer as this rare malignancy occurs almost exclusively in uncircumcised men. Human papilloma, which can hide under the foreskin, is associated with cervical cancer—women diagnosed with it are more likely to have an uncircumcised sexual partner.

Health Impact

Removal of the foreskin which toughens the skin of the glans, has been theorized to have many additional beneficial effects. In addition to possibly preventing the cervical cancer caused by sexual contact, it appears to prevent penile cancer, a rare malignancy affecting about 1,000 men in the United States—patients are almost exclusively uncircumcised men. Furthermore, in uncircumcised infants, UTIs have been shown to be more common, perhaps because the moist environment under the foreskin can harbor UTI bacteria. In those particularly vulnerable (e.g., boys with congenital urinary anomalies, such as posterior urethral valves, prune belly syndrome, vesicoureteral reflux, and hydronephrosis), circumcision might be a way to decrease the risk of UTI.

Current Clinical Practice

Phimosis can be treated in three major ways. First, the foreskin can be removed by circumcision. Serious complications are rare and may include bleeding, infection, or damage to penis. Second, the dorsal foreskin can be slit to retract it more easily. Some families prefer this because the

patient is technically uncircumcised. Finally, topical corticosteroid cream (0.05-0.1 percent betamethasone) applied to the penis can loosen the scarring in mild and moderate cases. Circumcision rates have changed with time and reflect population and socioeconomic shifts; in the United States, there are regional differences, with the Northeast and Midwest having the highest circumcision rates of newborns.

Given the potential benefits of circumcision, some researchers call for a change in the official American Academy of Pediatrics policy, which currently does not go so far as to recommend it as routine practice. However, opponents of routine circumcision point out that STDs occur in circumcised men and that STD prevention depends more on promoting safe sex practices. Furthermore, other factors are associated with penile cancer besides circumcision, and penile cancer incidence in societies with low circumcision rates and high levels of hygiene is comparable to that in societies with high circumcision rates. The UTI risk studies were nearly all retrospective and may have been skewed by other risk factors such as vesicoureteral reflux. Another factor that must be weighed in the balance is complications from circumcision; while the complication rate is very low, disastrous outcomes such as total loss of the penis are possible. Routine circumcision in the population would mean that thousands of children would be placed at risk to prevent just one case of cancer.

Priorities for Research

- Prospectively study the effect of neonatal circumcision on UTI frequency using cohort matched groups in a statistically sound longitudinal study. Two arms of investigation could be males with no genitourinary anomalies and males at increased risk from genitourinary anomalies.
- Investigate the efficacy of surgical alternatives to complete circumcision such as the dorsal slit and corticosteroid creams.

- Study the effect of education of pediatricians and parents on the proper care of the uncircumcised penis, with the goal of preventing pathological phimosis.
- Investigate on an epidemiological basis the role of cultural influences and U.S. regional migration on decision making for or against circumcision.

19. Varicocele

Summary

Treating varicocele in adolescents to improve prospects for fertility in adulthood remains controversial. A prospective clinical trial to assess long-term outcomes (semen parameters, testicular growth, and fertility) of watchful waiting versus surgery is needed to permit rational therapy. Such a study could provide specimens, including serum and fractionated semen for identification of novel biomarkers, to predict fertility problems.

Varicocele, the abnormal dilation of the veins of the testis, occurs in approximately 15 percent of teenage and adult males. The major long-term concerns are impaired testicular growth and infertility. The pathophysiology of varicocele remains unclear. Some patients have compression of venous drainage associated with absent or poorly functioning valves of the testicular veins. This can result in increased testicular temperature bilaterally and be associated with increased bilateral testicular blood flow, a decline in intratesticular testosterone, and a decline in spermatogenesis, likely through increased germ cell apoptosis.

The future fertility status of the adolescent children with varicocele is not known. Thus, there is a need to determine which adolescents are at risk

and in need of intervention. Varicocele surgery successfully restores fertility in only 40 to 50 percent of infertile men who undergo repair. The possible advantage of earlier surgery should be investigated.

Health Impact

Affecting as many as 40 percent of infertile adult men, varicocele represents the most common clinical finding associated with reversible male factor infertility. The incidence in adolescents approximates that in adults (15 percent), and the long-term followup of these children entails enormous costs. Furthermore, tens of thousands of surgeries in adolescents with varicocele are performed annually, despite controversy as to whether they prevent infertility.

Clinical Description and Management

Varicocele most commonly occurs on the left side, but it can occur bilaterally and affect the function of both testes. The condition varies in severity, described by grades 1-3. Impaired growth of the affected testis can be seen in many boys with varicocele and may result in impaired sperm production. Fewer than 5 percent of patients experience testicular pain, and this can be relieved by surgery. Some families and children affected by varicocele suffer from worries about future fertility.

Varicoceles can be managed surgically and observationally; there is controversy as to whether surgery impacts future fertility. Impaired growth of the involved testis has been the most widely accepted criterion for surgical intervention. While size difference would appear to represent an objective and logical sign on which to base a surgical management decision, the reality is more complicated. After hypotrophy, a commonly used criterion for surgical correction has been a large varicocele. The adult data correlating varicocele size with fertility status would suggest that large grade III varicoceles correspond to lower

sperm counts and improved response to surgical correction of the varicocele.

It is rational to manage most adolescent patients with a varicocele by observation and regular followup examinations. Those who would clearly fall into this category would be boys with equal testicular volume and no symptoms, independent of varicocele size. In fully developed adolescent males, it is desirable to obtain semen analysis data when they are willing to comply.

Priorities for Research

Perform well-designed clinical study(s) to assess long-term outcomes of watchful waiting versus surgery for varicocele. Ideally, the study would:

- Determine whether early repair improves semen parameters, testicular growth, and fertility.
- Develop reference data of normative semen parameters in the fully developed male adolescent.

- Identify possible clinical and hormonal indicators that allow identification of adolescents at risk for infertility.
- Define clear indications for intervention to correct varicocele.
- Provide specimens, including serum and fractionated semen, for identification of novel biomarkers.
- Identify the molecular basis of testicular damage in varicocele by assaying for novel biomarkers from banked specimens, including testicular vein blood and fractionated semen.
- Exploit the use of animal models of varicocele to study factors that control testicular growth and the mechanisms by which varicocelectomy restores fertility.
- Assess the outcomes of testicular artery-sparing surgery versus other methods.
- Study the health benefit of educating primary caregivers and teens on varicocele to increase early detection.