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Dan Wood *Editors*

Transition and Lifelong Care in Congenital Urology

Humana Press

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Preface

The genitourinary tract is one of the systems most frequently affected by congenital defects. Such defects can be solitary (e.g., hypospadias) or involve multiple organ systems (e.g., myelodysplasia or cloacal exstrophy). In addition, patients with neurological conditions of childhood like cerebral palsy (CP) and neuromuscular diseases often have substantial urological comorbidity that is progressive with age. For a small subset of this group (e.g., exstrophy), the urologist is often the most knowledgeable care provider about the patient's condition, anatomy, and long-term medical risks. As such, the urologist may serve an important role in the facilitation of primary care role for some of these individuals. However, as these patients now are surviving to adulthood with excellent health, issues of sexuality, post-pubertal genital appearance and function, urinary and fecal incontinence, fertility, and pregnancy are becoming important health and quality of life issues. Many of these issues largely fall outside the spectrum of pediatric urological practice. Moreover, with aging and development of other medical comorbidities, patients with congenital anomalies experience typical urological age-related problems (like BPH and prostate cancer) that are often more complicated by their coexisting anomalies and prior operations.

Many patients who have these conditions will have undergone complex surgery. This represents a contract of care between parent, patient, and health-care systems—duty bound to provide lifelong care for these patients who are now surviving into middle life and beyond. This means that surgeons and others looking after these patients in adult life must have an understanding of both the conditions and their pediatric treatment in order to provide appropriate long-term care.

This book covers many of the most prevalent challenges for the urologist caring for adult congenital patients. The first part provides a framework for *transition to an adult care model* as well as a general approach to patients with three of the most common conditions encountered in congenitalism: myelodysplasia, hypospadias, and exstrophy. The remainder of the parts cover topics by anatomic category. Sexuality, fertility, and genital issues are discussed in Part II, followed by lower tract management issues in Part III, and finally upper tract management issues in Part IV. Part V addresses urological care of the pediatric cancer survivor.

We would like to extend our sincere appreciation to all the contributors to this book—their collective experience represents the only real "data" upon

which we can make treatment recommendations, since there is a dearth of scientific literature in this area. In addition, we would like to thank Patrick Carr for his persistence and skill in bringing each chapter to life. And finally, we would like to thank our mentors and friends, Eric Klein, M.D. and Professor Christopher Woodhouse, for their support and encouragement for this project and in our careers.

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Part I

Overview

The Transition Process: Initial Assessment and Development of a Treatment Plan

1

Hadley M. Wood and Elizabeth B. Yerkes

Introduction

Young adulthood is well recognized as a time of life with low utilization of health care and preventive services. Economic and social norms of the past have been in part to blame. In the US prior to 2010, insurance coverage through state-funded Child Health Insurance Programs and dependent coverage through private insurers often ended at age 18 or 21. If the emerging adult (age 18–25) has a health condition from childhood, insurance coverage was historically even more difficult or expensive to obtain. The Affordable Care Act (ACA), in mandating dependent coverage up to age 26, expanding health care options for lower income patients, and expanding care options for patients with preexisting conditions, has facilitated health care provision to many emerging adults with special health care needs.

Access aside, transition from a pediatric care model to an adult-care model requires that the patient assume responsibility for independently accessing health care providers, understanding and implementing health care plans, and communicating changing conditions back to those providers. This is all done within the context of a period of life traditionally subjective to risky health behaviors, including experimentation with drug and alcohol use and sexuality. *The goal of transition is to provide uninterrupted, developmentally appropriate transfer of medical care to an adult-care model*. Achieving this goal requires establishing a step-wise process whereby the patient is assessed for transition readiness regularly, transition is planned by engaging the patient and all stakeholders, and then care is transferred to the new care team. The US Department of Health and Human Services has incorporated this process into the core elements of Health Care Transition (Fig. 1.1).

The costs associated with non-transition of this population are both financial and human. Human costs include lost productivity of caregivers of persons with disabilities as well as lost productivity of the patients themselves. Caregivers of myelomeningocele patients reported a reduced productivity of 6.2–13.3 h per week [1]. Financial costs to the health care system, although poorly quantified, are substantial. These come in the form of increased costs of reactive versus preventative care, increased morbidity of disease, and increased utilization of costly emergency services. Estimates suggest that 34–47 % of admissions for adult myelomeningocele patients were for potentially preventable conditions, including

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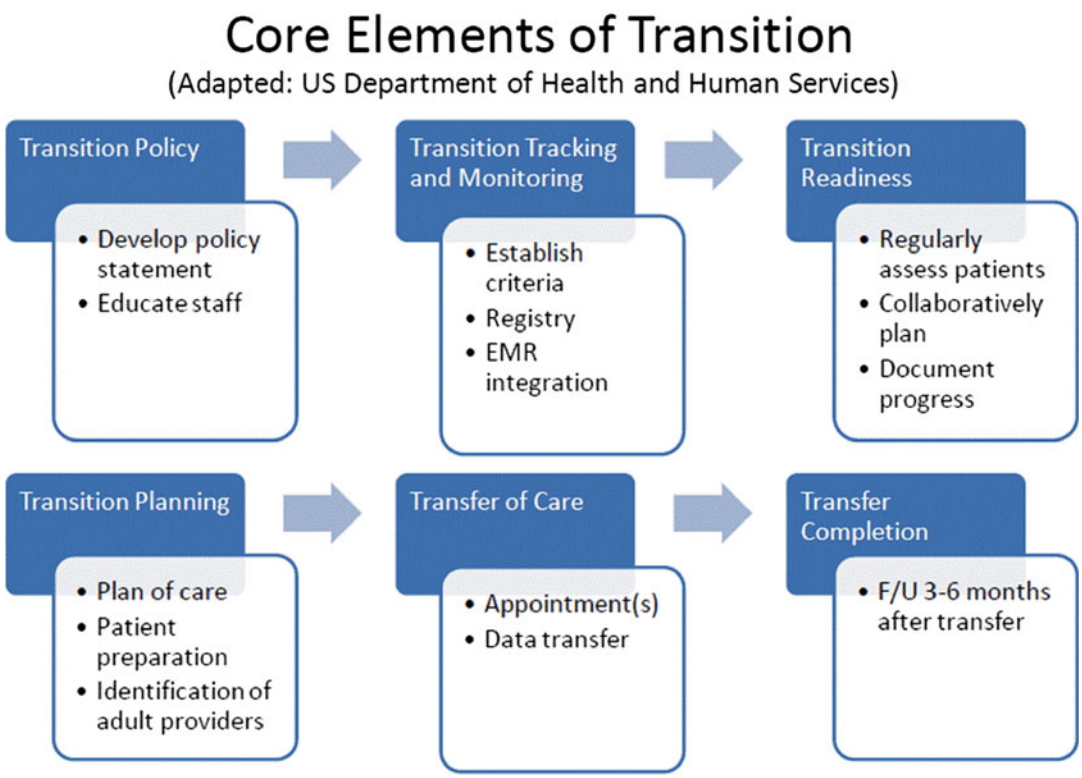

Fig. 1.1 Summary of the recommended steps for transition of care

urinary tract infections and wound problems. These estimates amount to approximately $364 M over a 2-year period [2, 3]. In an era of ever-expanding costs, focused preventative care of this population may provide reduced financial burden on the health care system and improved overall quality of life for patients.

The public health industry recognizes that lack of coordinated transition leads to substantially increased medical and societal costs and therefore has supported implementation of transitional programming in many public policies. The ACA has called transitional services as an "essential health home service" and the US Health and Human Services identified transition as one of six core performance outcomes necessary for comprehensive care of children with special needs. Despite a substantial amount of public health resources aimed at bolstering transition of care for emerging adults with special needs, it is estimated that only about 40 % of this patient group met the national standard for transition of care [4], a number that has shown essentially no improvement over the past 4 years [5]. As of 2005, 76 % of adults with chronic congenital anomalies did not have or could not identify a primary care doctor [6].

While the bulk of the burden of transition rests with the primary care provider, the urologist is not immune. The genitourinary tract is one of the systems most frequently affected by congenital defects. Such defects can be isolated (e.g., hypospadias) or involve multiple organ systems (e.g., myelodysplasia). In addition, patients with neurological conditions of childhood like cerebral palsy (CP) and neuromuscular diseases often have substantial urological comorbidity that is progressive with aging. For a small subset of this group of transitioning individuals (e.g., those born with exstrophy), the urologist is often the most knowledgeable care provider about their condition, anatomy, and long-term medical risks associated with the disorder. As such, the urologist may indeed serve an important role in facilitation of

primary care needs for some of these individuals. An additional two subgroups that should be considered for transition are survivors of pediatric and pelvic cancers and renal transplant recipients. While these individuals may not have primary congenital urological issues, their urological needs in adult life may be very different from those in pediatric life, a long-term result of their childhood medical story, and they may have delayed acquisition of adult milestones of independence [7].

Traditionally, the pediatric urologist has served this diverse population throughout childhood and adulthood. Pediatric urologists are well equipped to do so with their knowledge and experience with congenital anatomy, their lifelong relationships with the patients and families, and focus on integrative care. However, as these patients now are surviving to adulthood with excellent health, issues of sexuality, postpubertal genital appearance and function, urinary and fecal incontinence, and fertility and pregnancy become increasingly important health and quality of life issues. Moreover, with aging and development of other medical comorbidities, patients with congenital anomalies experience typical age-related urological problems, such as BPH and prostate cancer, which are often complicated by their coexisting anomalies and prior operations. The field of urological congenitalism requires a knowledge base and skillset that pool the assets of both pediatric and adult urology (Fig. 1.2).

While the approach to a typical adult urological patient is one problem: one solution, the patient with a congenital urological problem rarely presents in that manner. These patients have a lifelong history of treatment by other medical care providers and those experiences, both good and bad, often influence their expectations. Other limitations, including ambulation status, cognitive deficits related to lifelong hydrocephalus (for some), or nutritional challenges may make treatments more difficult or risky. Finally, these individuals may have variable dependence on other care providers at home and in the community, so it is critical to ensure that their input is part of the initial assessment. For some who have had a parent assist with self-care for their whole lives, the aging parent may be dealing with his/her own medical and physical constraints as well as the (often unspoken) distress about who will care for their child in the future.

As such, one should provide adequate time for careful consideration of the problem, patient education, and consideration of the patient's and family's needs (Fig. 1.3). Every evaluation should follow a step-wise approach. These include: (1) defining the patient's baseline, (2) understanding the patient's goals, resource constraints, executive and cognitive assets and deficits [8, 9], and social constraints, (3) characterizing the "new" or "worsening" complaint, (4) determining the appropriate diagnostic tests to define the problem, and (5) developing a menu of treatments that will address the concern and delineating the associated personal "costs" or risks of each. Oftentimes, development of a care plan may involve careful negotiation, a substantial amount of investment of time educating the patient about expectations, and communication with other medical providers.

Step 1: Defining Baseline

While the population about which we write is heterogeneous, most will require a baseline assessment of urological function. This includes renal function, continence status/use of protective garments, urinary infections, sexual function and activity, fertility (past and present), and prior urological medical and surgical treatments. Assessment of renal function may be symptom based, require noninvasive evaluation like renal ultrasound and serum electrolytes, or may be more involved. For those with neurogenic bladder, whether related to spinal dysraphism on non-neurogenic bladder dysfunction related to posterior urethral valves or exstrophy complex, baseline function is ideally established using urodynamics or video urodynamics and then followed symptomatically and with periodic repeat studies every 2–5 years depending on baseline results. For patients with continent pouches who may have some baseline renal insufficiency, involvement with a nephrologist early is helpful to help manage complex metabolic challenges

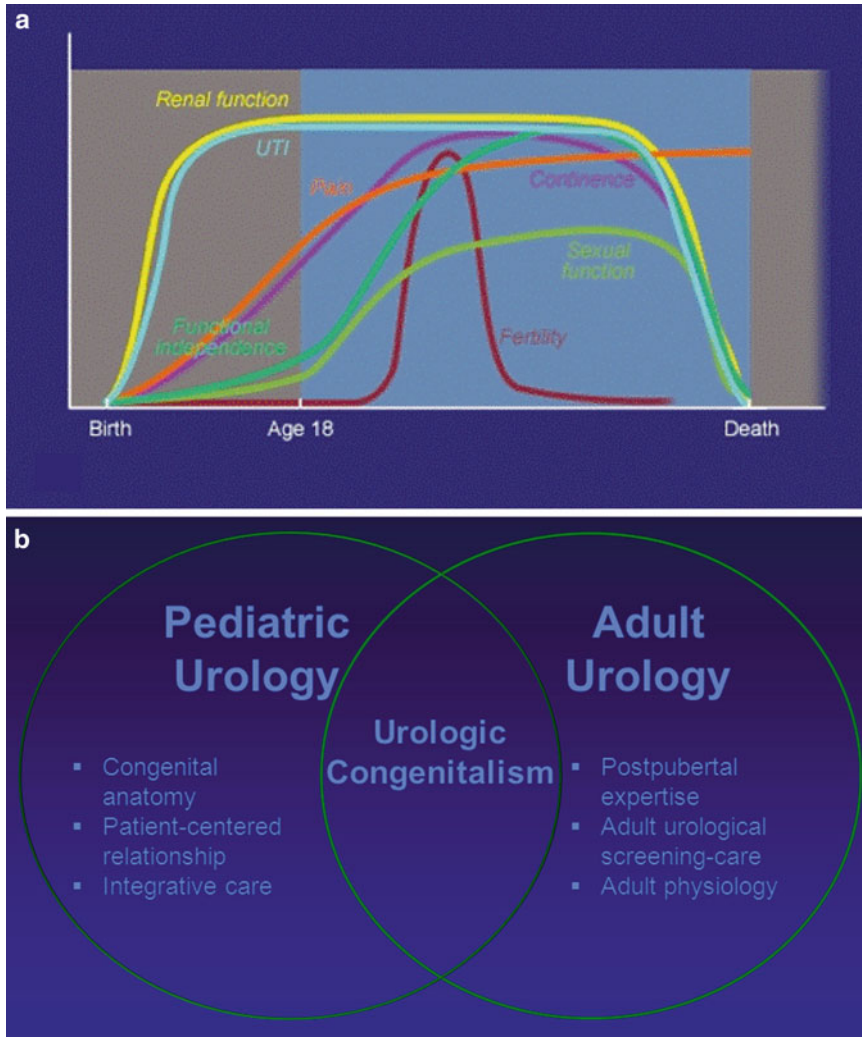

Fig. 1.2 (**a**) Graphic portrays relative importance of urological needs for a male patient with myelomeningocele throughout his lifespan. (**b**) The field of urological congenitalism combines the specialty skillset of pediatric and adult urology

and secondary problems related to chronic acidosis and chronic kidney disease (CKD). It is now well recognized that renal insufficiency at all stages has substantial downstream effects, including increased systemic inflammatory markers and lipids, and results in higher all-cause mortality and cardiac mortality [10]. Slowed progression of CKD may not only prevent the burden and cost of renal replacement therapy (RRT), but may also prevent early death due to cardiac disease. Consideration of non-creatinine-based methods of estimation of GFR (iothalamate renal scan or cystatin C) may be warranted for patients for whom creatinine production is not normal; for example, patients who are non-weight-bearing, have short stature, or atypical body habitus.

Urinary continence and urine management with catheters often changes as a young person progresses through puberty, related to weight gain and other factors. Moreover, the social implications of incontinence may also change. This is particularly relevant for young individuals who are progressing from a home environment to a shared-living environment such as a college dorm. Understandably,

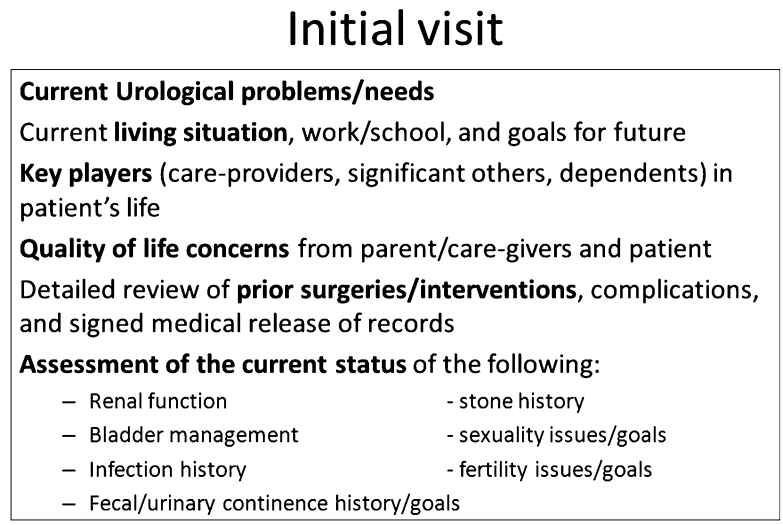

Fig. 1.3 Summary of key components of initial evaluation of an adult with congenital urological needs

compliance with self-catheterization may be difficult when a new living situation does not allow the individual to do this discreetly. Assistance with troubleshooting these challenges is relevant for some of our emerging adult patients.

For many patients transitioning to adult care, issues of sexual function and fertility may be of paramount concern. Many of these individuals will not have discussed these topics openly with their pediatric providers, even if sexual health topics were raised at annual visits. The urological congenitalist plays an important role in sexual counseling, particularly for the latex-sensitive patient or a female patient with a urinary reservoir who present a unique pregnancy risk, and optimization of sexual function. Female patients who are on prophylactic antibiotics for UTI prevention and sexually active should be assessed for the continued need for prophylaxis, and counseled regarding the least teratogenic prophylactic antibiotic available. Likewise, young women affected with myelodysplasia should also be counseled to be on high dose folate (4,000 μg) throughout reproductive years regardless of their intention to become pregnant. Vaginal and uterine anomalies are common among women with cloacal malformation or cloacal exstrophy and may require counseling related to expectations for pregnancy. Many female patients with complex urological disease who choose pregnancy will require collaboration with Maternal Fetal Medicine regarding adequate bladder drainage and delivery strategies. For men, particularly those with genital abnormalities (hypospadias, exstrophy-epispadias complex), sexual dysfunction may extend well beyond erectile dysfunction. Baseline semen analysis should be offered to young men with history of undescended testicle and hypospadias, as well as others who may be at elevated risk for infertility.

If appropriate, patients should be screened for bladder or colon cancer. Patients identified to be at highest risk for lethal bladder cancers include those with augmentation cystoplasty or continent diversion and prior renal transplant/viral cystitis, more than four UTIS per year, gross hematuria, pelvic or bladder pain, radiographic abnormality seen, or history of bladder exstrophy. The lifetime risk is estimated to be 1.2–4.6 %, with a median time to tumor development 19–32 years [11, 12]. Patients with gastrocystoplasty and those who have had prior or existing ureterosigmoidostomies have special cancer screening considerations as well (see Chap. 11). Optimal screening recommendations for these special populations have yet to be developed.

Baseline bowel function also merits evaluation because of the strong effect it has on urinary continence and UTI risk, and because some congenital neurogenic patients have less frequently accessed care through adolescent and early adult years. Some may require surgical management if the colon has been permanently affected from lifelong distention. Success of prior and current use of stool softeners, oral stimulant laxatives, fecal

disimpaction or digital stimulation, and antegrade or retrograde enemas or suppositories should be documented to guide effective management.

Step 2: Understanding the Patient Goals and Resource Constraints

Many patients come to an adult urology clinic with clearly identified goals, which may be different from the goals of the provider. This is especially true for the congenital patient, for whom questions about sexual function, fertility, or genital appearance may have been purposefully or involuntarily deferred in pediatric life when under the watch of parents or caregivers. On the other hand, renal preservation and other issues that may be deemed more "pressing" by a treating physician may be at the top of the physician's mind in developing a treatment plan. It goes without saying that taking the time to hear the patient's concerns and limitations, as well as being clear about your own medical opinion, is critical to ensuring that the patient feels satisfied. It is also important for the provider to infer whether the substance of the conversation is understood or simply accepted politely.

In addition, treatments which may be considered "standard" for one patient may not be reasonable for another in a different environment. For example, for a patient with an obstructed urethra in a wheelchair, a suprapubic tube may impair a patient's ability to be mobile or transfer from his chair, or if he has limited lift-assist in his daycare environment, a perineal urethrostomy may result in high risk for urinary accidents and ulcer formation. For this reason, a clear understanding of what the patient's care and support environment is both day and night is mandatory in determining which options may be on the table for an individual who requires assistance. Treatments should emphasize patient independence and competence with self-care, with avoidance of treatments that may result in outcomes that can be further disabling. Unless a patient is critically impaired with limited duration of life, an indwelling urethral catheter should never be considered a long-term option for urinary management.

Step 3: Characterizing the "New" or "Worsening" Complaint

While pediatric patients are growing and potentially changing urologically over time, adult patients tend to have more stable presentations. A new or worsening complaint should be recognized as a marker of changing physiology and should warrant complete investigation. For many individuals with congenital urological problems, escalation of urinary infections or worsening leakage problems are the most common reasons for visits to the urologist. Because many factors influence both these problems, full characterization of all risk factors for both may help direct diagnosis. For example, an individual with congenital neuropathic bladder on intermittent catheterization who is experiencing escalating frequency of infections may be due to behavioral factors (noncompliance with catheterization or bowel regimen, hygiene, sexual intercourse), medical factors (increased susceptibility from immunosuppression by medications), or surgical factors (bladder stones, diverticulum, fistula, etc.). Characterization of such a problem requires a review of symptoms, behaviors, medications, recent and distant medical and surgical problems, and a complete physical exam.

Step 4: Determining the Appropriate Diagnostic Tests to Define the Problem

This step seems self-explanatory. However, it is important to note that diagnostic evaluation should be driven by unique patient physiology. Some patients may require special positioning for testing due to anatomic limitations or may require additional interventions to fully characterize a problem. For example, while placement of a Foley catheter is not standard for adult patients undergoing nuclear renal scan, a patient with known or suspected VUR should have a catheter placed in order to accurately assess upper tract drainage. Individuals with CKD may have limitations in terms of imaging options as well.

Step 5: Developing a Menu of Treatments that Will Address the Concern and Delineating the Associated "Costs" or Risks of Each

Finally, and most importantly, congenital urological patients often have multiple, sometimes competing, urological and medical needs. Treatment of one may represent a risk to another. For many of these patients, surgery is more likely to result in morbidity and will require longer to recover than for an otherwise healthy patient. For a patient with prior heart valve replacement and recurrent UTIs, nontreatment and subsequent urosepsis may represent a risk for infectious endocarditis, while treatment may require a patient stop anticoagulants and therefore present a risk for thrombotic events. Consideration of the whole patient and all the associated risks of treatment require medical knowledge and careful evaluation of the medical and surgical history followed by an in-depth discussion of the potential benefits and pitfalls of each treatment paradigm.

A transition plan for emerging adults with congenital or acquired urological conditions is challenging but essential. They are entering a phase of personal development, perhaps with new autonomy in decision-making, liberty to forge new social relationships, and willingness to discuss concerns related to sexual health. These liberties coexist with ongoing medical needs but potential risk-taking behaviors. Many, particularly those with myelomeningocele and hydrocephalus, will have limited experience with self-management or limited executive or cognitive assets to help them own these adult-type steps, but there is evidence that their psychological health is linked to competence with self-care [7–9, 13].

Most pediatric urologists feel a strong commitment to their patients with congenital urological anomalies, as they have invested energy and watched them grow and shepherded both the individual and family through difficult times. That said, many also recognize that the physical, medical, and psychosocial transition to adulthood will bring concerns that deserve long-term urological care with a capable caring adult urologist. Details of prior care, particularly relevant reconstructive details, may not be adequately recalled by the patient and family caregivers. With this investment in mind, obtaining a transfer summary and surgical records should be routine or available upon request. Scheduling the initial visit to allow adequate time to fully assess the global situation and to formulate a preliminary plan is essential for the urologist accepting care of these complex individuals.

Summary

The goal of transition is to provide uninterrupted, developmentally appropriate transfer of medical care to an adult-care model.

Evaluation of a patient should include a thorough history, review of prior medical records, and include the following steps:

1. Define the patient's baseline urologic and nephrologic function.
2. Understand the patient goals and resource constraints.
3. Characterize the "new" or "worsening" complaint.
4. Determine the appropriate diagnostic tests to define the problem.
5. Develop treatment plan that will address the concern(s) and delineate the associated "costs" or risks of each.

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Approach to the Myelodysplasia Patient

2

Rosalia Misseri

The Spina Bifida Association reports that 7 of every 10,000 children born in the United States have myelomeningocele (MMC) and that there are more than 166,000 people currently living with MMC [145]. Today, survival into adulthood is reported as high 85 % (at age 34 years, 94 % of those without shunts, and 75 % of those with shunted hydrocephalus are alive) [32]. With decreases in birth prevalence of MMC after the introduction of prenatal diagnosis and mandatory folic acid fortification of grain products in the United States, there may be more adults currently living with MMC in the United States than children [23, 32, 59, 107, 136, 140, 161]. Despite a large number of people living with MMC, there are no randomized controlled trials regarding urologic care in this group, and there is a paucity of literature describing long-term urologic outcomes in adults with MMC [153].

Children born with MMC are very readily identified. Many children have been diagnosed antenatally and few have had closure of the spinal defect before birth. MMC results in varying degrees of disability including paraplegia, orthopedic and neurologic abnormalities, and bowel and bladder dysfunction. Cognitive function may be affected in varying degrees as well. Once born, these children are promptly treated for their neurologic lesions by pediatric neurosurgeons and are quickly evaluated by the multiple subspecialists that will carefully monitor their progress and treat them over the course of their childhood. This group of medical specialists often includes developmental pediatricians, pediatric neurosurgeons, pediatric neurologists, pediatric physiatrists, pediatric orthopedists, and pediatric urologists. Many centers offer meticulous and successful multidisciplinary care for the child with MMC.

Such meticulous care has led to much advancement in the management of MMC. As survival of those affected has improved, concerns over transition of youth to adulthood and care for the adult with MMC have increased. Transition of care has been advocated by many individuals and multiple organizations. Each has identified variable important components and potential barriers to the ideal process, consequently a good model transition/transfer of care remains elusive [3, 4, 17, 49, 51, 52, 114, 121].

Earlier studies have shown that up to two-thirds of adults with MMC do not routinely seek regular urological follow-up [60]. Bladder function may change with aging and complications after reconstruction may occur into adulthood. Little is known of urologic outcomes after transfer of care and the majority of literature evaluating the neuropathic bladder in the MMC patient focuses primarily on pediatric patients. In a center

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with an established adult MMC clinic, Cox et al. found that the experience at the adult MMC clinic and the patients' perspective on the transition process were independent of urological and neurosurgical medical outcomes. Additionally, caregivers preferred the care received at the pediatric center [29]. Regardless of patient/caregiver sentiment, concerns that arise with aging such as those associated with sexual function, fertility, benign urologic disease (e.g., BPH), and screening for urologic cancer may be better addressed by "adult" urologists. Successful transition/transfer programs will likely require formal exchange of medical records including past management strategies such as catheterization schedules, need for anticholinergics, attention to the upper urinary tract, prior surgeries, and surgical reconstruction. For successful transfer, the patient must be agreeable to the change and the accepting urologist must be interested and knowledgeable in the care of the aging MMC patient regardless of the patient's level of function or dependency on a caregiver.

Evaluation

Careful attention and preservation of renal function remain most important across the lifespan. It remains the responsibility of the urologist, adult or pediatric, that this is not forgotten. Those with untreated neuropathic bladders secondary to MMC are at risk for complications including urinary tract infections, urinary incontinence, and deterioration of the upper urinary tract with potential loss of renal function. Most urologists would agree that the management of the neuropathic bladder and the reconstructed urinary tract require yearly and lifelong follow-up [2, 63, 116, 147, 153, 164]. This would include physical examination, renal ultrasonography, abdominal radiograph, and serum creatinine measurement. Despite this general agreement, there are no standardized recommendations for the follow-up interval or what follow-up would involve [13, 116, 151, 155]. In a systematic review of people with MMC over 18 years old, Veenboer and colleagues found that 58.4 % performed CIC, 13.8 % voided normally, 10.5 % had incontinent diversions, 5.9 % had complete incontinence, 4.3 % had an indwelling catheter, and 2.9 % empty by Crede [153]. This heterogenous group may contribute to the difficulties of standardizing follow-up protocols.

The European Association of Urology (EAU) Guidelines on Neurogenic Lower Urinary Tract Dysfunction recommends urodynamics (UDS) every 1–2 years [112]. In a recent study, Veenboer et al. reported that unfavorable urodynamic findings are very unlikely in asymptomatic individuals who are not wheelchair bound. They concluded that it is probably not necessary to perform UDS as frequently as is currently recommended by the EAU [155]. UDS may be most useful if new symptoms, e.g., urinary incontinence, increased leakage between catheterization, and recurrent urinary tract infection, occur. Unfortunately, as management protocols differ and follow-up differs, the effects of intervention and evaluation remain largely unclear.

Attention to Renal Function

Since the introduction of the ventriculoperitoneal shunt (VPS), renal failure and its consequences became a leading cause of mortality in children with MMC surviving infancy, accounting for 20–30 % of deaths [61, 93, 141, 164]. Renal function is typically normal at birth, but may deteriorate over the patients' lifespan due to the functional abnormalities of the neurogenic bladder and/or recurrent infections [44]. Untreated, up to 50 % would develop chronic kidney disease (CKD) [165]. Urodynamic risk factors for the development of CKD include detrusor sphincter dyssynergia, detrusor overactivity, high detrusor leak point pressure, and high intravesical pressure. UTIs in childhood were also linked to renal dysfunction later in life [63, 150]. Thirty to forty percent of children with myelomeningocele have been reported to have some renal impairment [18, 105]. In an analysis of 52 adults with lumbar myelomeningocele, Persun and colleagues found that only 38 % had a normal ultrasound and a serum creatinine level less than 1.5 mg/dl despite

performing CIC and being dry between catheterizations [116]. In a systematic review, 72 % of people with MMC were found to have well-preserved function, 25.7 % with CKD stages 1–5, 1.3 % with ESRD. Up to 20 % were found to have VUR [153]. Veenboer estimates that ESRD was the cause of death of 8.9–28.6 % of the patients included in the review [153]. In a cohort of children born in the modern medical era, i.e., after the introduction of CIC for bladder emptying and widespread use of anticholinergics, Misseri and colleagues found renal failure was a rare cause of death in people with MMC after bladder augmentation. Mortality from renal failure was 0.5 % at 10 years after augmentation, lower than historical cohorts. The most common cause of death was non-urologic infection [98, 99]. In a separate birth cohort of 160 children with MMC managed in the modern era, no deaths were observed related to renal failure by age 20. This supports the notion that death from renal failure in well-managed MMC is now rare [91].

Estimated GFR (eGFR) using serum creatinine has been most commonly used to determine renal dysfunction in the MMC population. However, because of low muscle mass and underdeveloped musculature of the legs, creatinine-based methods to evaluate renal function are of poor sensitivity in this group. Once an abnormal serum creatinine level is noted, a loss of more than two-thirds of nephrons may have already occurred [119]. In the general population, the American Society of Nephrology suggests referral to a nephrologist if the estimated glomerular filtration rate is 60 mL per minute per 1.73 m^2 or less (stage 3 chronic kidney disease) or if macroalbuminuria is present. However, no specific recommendations exist for patients with MMC. Cystatin C- or iothalamate-based eGFR may assess global renal function in this group of patients, but this is not widely available for clinical use [117]. Despite its ability to estimate GFR, these modalities have never been compared with each other or with creatinine-based methods for MMC patients. In addition, these methods do not provide any information on renal scarring [1]. This knowledge is best gained with dimercaptosuccinic acid (DMSA) scan. Up to 25 % of people with MMC have been reported to have scarring on long-term follow-up. A history of vesicoureteral reflux history and febrile urinary tract infections were most commonly associated with abnormal DMSA scan in follow-up of patients older than 10 years with MMC [137].

Careful attention to changes in continence, recurrent UTI, weight gain, hypertension, and urolithiasis is very important as they may independently affect renal function. In addition, some of these conditions may also indicate a change in bladder dynamics. Each may ultimately lead to upper tract changes and renal disease. With each episode of pyelonephritis, nephrons are lost and renal failure may ensue. Antibiotic prophylaxis may be helpful in carefully studied patients. Kidney stones are also a risk factor for CKD and progression to ESRD [127]. Screening for and treatment of hypertension is important as well. Treatment with angiotensin-converting enzyme inhibitors may prevent progression to CKD [65, 162].

Attention to Bladder Function and Continence

Changes in continence, recurrent UTI, and urolithiasis are important indicators of bladder dynamics. Worsening continence may be related to poor adherence to catheterization schedules or anticholinergic use, changes in bladder function, or tethering of the spinal cord (though less common after periods of rapid growth) [164]. Incontinence of urine affects many life domains including the physical and the emotional. Skin breakdown, infection, poor self-esteem, social isolation, and underemployment/unemployment are often a consequence of incontinence [104].

Anticholinergics

Since the 1980s, “proactive” management of the neurogenic bladder has included CIC and anticholinergic therapy starting at in infancy [36, 41, 44]. The necessity of long-term anticholinergics and the effects of long-term use of this class of

drugs have not been critically evaluated in adults. However, evidence suggests that management with CIC and anticholinergics through puberty may result in improved maximal bladder pressure, bladder capacity, and detrusor leak point pressure in adults [2]. The most commonly used anticholinergic in children is oxybutynin both for its efficacy in the treatment of detrusor overactivity and urinary incontinence and because it is the only anticholinergic to be approved for use in children by the U.S. Food and Drug Administration. Oxybutynin is a nonspecific antimuscarinic agent blocking M1, M2, and M3 receptors. In blocking efferent parasympathetic M3 receptors innervating the detrusor muscle, bladder contraction is inhibited. Many side effects encountered by patients are due to its nonspecific nature. Due to its high lipophilicity, neutral charge and small molecular structure, oxybutynin crosses the blood–brain barrier. The side effects of anxiety, somnolence, hallucinations, and cognitive dysfunction are related to its action on the M1 receptors in the brain [154].

Concerns regarding cognition in adults using anticholinergics have recently been raised; however, little is known regarding long-term use in people with MMC whose use often begins in childhood. Only one study has examined behavior and long-term use of anticholinergics in children with MMC. Veenboer and colleagues explored possible associations between long-term antimuscarinic use (from birth to median age 10.6 years) and behavioral problems in children with MMC and neurogenic bladder. No significant differences in behavior between children with MMC with and without long-term use of antimuscarinics were found [154]. In a double blind, placebo controlled crossover study, the use of anticholinergics was found to impair cognition in older adults without MMC [70]. A subsequent systematic review and meta-analysis could not determine if antimuscarinics effect CNS function since standardized measurement of age-stratified CNS outcomes are lacking [113]. Two pediatric case–control trials have examined the effects of oxybutynin on cognition and short-term memory in neurologically intact children and neither study has found any untoward effects on short-term memory of cognition [53, 143].

Recurrent Urinary Tract Infection

Despite improvements in the management of the neuropathic bladder with respect to renal preservation, the incidence of urinary tract infection in people with MMC remains very high and continues to be a common cause of morbidity and impaired quality of life for patients with MMC. Unfortunately, definitions for UTI are variable and are infrequently applied in studies resulting in difficulties assessing the true UTI rates in this group [90]. Filler and colleagues report that up to 50 % of children will experience a UTI by 15 months and 44 % will have more than 5 UTIs by age 15 [46]. Other studies have demonstrated that the annual incidence of UTI in patients with neurogenic bladder is as high as 20 % [160]. The high incidence of UTI may be associated to intermittent catheterization, incomplete emptying, constipation, anatomic abnormalities, and calculi. Due to altered sensation, people with MMC may not have typical symptoms of UTI [166]. By the time most patients reach adulthood they are well aware of individual, specific symptoms that indicate UTI, e.g., lethargy, headache, increased mucous production. Differentiating asymptomatic bacterial colonization from true infection is important particularly in people performing CIC [132]. Cautious therapy of positive cultures is important to help prevent multi-drug-resistant organisms in this patient population. Treatment with multiple courses of antibiotics may lead to more virulent bacteria and a requirement for more toxic antibiotic treatments.

Catheterization

Clean intermittent catheterization is often introduced very early in life and remains necessary throughout the entire lifetime of a patient with

MMC. It is generally well accepted and becomes routine both for the child and his/her caregivers [44, 85]. Hematuria, false passages, urethral stricture, and epididymitis may occur as a consequence of repeated and long-term catheterization. Reports of such complications range from 0 to 40 % [20, 167].

Over a median of 16 years, Lindehall and colleagues found 25 % of boys had major urethral complications including false passage, urethral stricture, and metal stenosis. To prevent complication, the authors recommend the use of as large a catheter as the urethra can accept and to start training children in self-catheterization early [84]. The use of lubrication may also decrease the complications associated with catheterizations. In a similar study reviewing the complications in young females, the authors found very few complications. These included gross hematuria, temporary difficulty catheterizing, and urethral polyps in two patients. Difficulty inserting the catheter and hematuria resolved spontaneously or by the use of lubricant [86]. With aging, progression to wheelchair-bound status, increasing independence, and weight gain associated with adulthood, some patients (particularly females) may have increasing difficulty accessing their urethra for CIC, which may require formation of a catheterizable channel or supravesical diversion.

Mobility

Mobility is affected in most people with MM and is an important determinant of quality of life [134]. The ability to ambulate is affected by the level of the lesion and often deteriorates over time. Decreased ability to ambulate appears to be related to a deterioration of the neurologic level of the lesion, increased spasticity, contractures of the knee and hip flexors, back pain, and lack of motivation. Major medical events such as surgeries, stroke, and lower limb edema were also found to contribute to the decline in ambulation [9].

Weight

Limitations in mobility, orthopedic deformities, cognitive impairment, and psychosocial issues may lead to an inactive lifestyle and resultant obesity. Dosa and colleagues found the obesity rate among adults with MMC at 37 %. This is more than twice the rate for children and adolescents with MMC. Extreme obesity was found in 11 % of adult women and 4 % of adult men with MMC [42]. Obesity may lead to further deterioration in function due to a decline in ambulatory status, difficulties with transfers, wheelchair propulsion, increased risk of pressure sores and other obesity-associated complications [6]. Obesity is a strong and independent risk factor for urinary incontinence in women and may contribute to worsening continence in MMC [159]. Peristomal hernias may occur in those with urostomies. Revisionary surgery and recovery becomes increasingly difficult in the obese patient.

Dexterity

Upper limb function is impaired in about two-thirds of children with MMC and may worsen with aging. These motor deficits include weakness, hand and finger dexterity, motor speed, and bimanual coordination [37]. Difficulties with dexterity increase dependence on others for activities of daily living including catheterizations.

Memory

Functional independence in people with MMC may be diminished due to problems with memory and deficits in executive function, e.g., planning, initiating, problem solving, affects [37, 89]. These deficits may be related to hydrocephalus, shunt malfunction, Chiari Type II malformation, dysgenesis of the corpus callosum, hypoplasia of the cranial nerve nuclei, gray matter ectopia, and diffuse microstructural anomalies [24, 38]. Such

difficulties may lead to poor adherence to catheterization schedules, medication regimens, and follow-up.

Postsurgical Considerations

Bladder Augmentation and Diversions

Bladder augmentation is a widely used and successful surgical option for the neuropathic bladder when medical management has failed. With refinements in medical management and improved techniques for augmentation, urinary diversion is rarely used [100]. Augmentation leads to improvements in continence, bladder capacity, and upper tract changes such as reflux and hydronephrosis/hydroureteronephrosis secondary to the hostile neuropathic bladder [26, 76, 88, 120]. A reduction in the incidence and severity of symptomatic urinary tract infections has been reported, and even when reflux persists, Krishna and colleagues found no evidence of deterioration of the upper tracts or progressive renal scarring [75]. Urinary tract reconstruction has been shown to lead to improvements in quality of life, self-image, self-esteem, and the ability to cope in women with neurologic impairment [158].

Despite the benefits, augmentation is a major surgical procedure with significant long-term surgical and nonsurgical complications. The most common and serious surgical complications are at the bladder level and include chronic bacteriuria, mucus production, formation of bladder calculi, metabolic abnormalities from exposure of the bowel to urine, bladder perforation, bowel complications, and the potential risk of bladder or bowel patch malignancy. Despite improvements in technique and advances in tissue engineering, the ideal technique and tissue for bladder augmentation and the creation of a functional bladder remain unknown.

Given that potential complications may occur at any time after surgery great care is mandatory when identifying and counseling surgical candidates. Lifelong attention to the surgically altered urinary tract is imperative. In a review of the first 500 bladder augmentations performed at Indiana University, complications were identified in 169 patients (34 %) resulting in a total of 254 surgeries. The cumulative risk of further surgery at the bladder level was 0.04 operations per patient per year after augmentation [94, 95].

Stones

Bladder calculi are increasingly recognized as a complication of bladder augmentation, affecting 11–52 % of patients and usually requiring an operative procedure [14, 35, 92, 94, 95, 109]. Stones tend to form in bladders that are incompletely emptied via catheterizable channels, those augmented with ileal or colonic segments rather than stomach and those made using absorbable staples [67, 77]. Recurrent urinary tract infections and noncompliance with irrigations, catheterizations and routine follow-up are other potential predisposing factors [27, 71]. While most stones are considered to be infectious, up to 30 % of cultured bladder calculi have been found to be noninfectious [98, 99]. This may be related to metabolic abnormalities such as chronic acidosis related to the augmentation or to chronic kidney disease. Hypercalciuria from osteodystrophy related to wheelchair dependence and poor mobility may also contribute to the high rate of calculi. Once a bladder stone is treated, the risk of recurrence is high, ranging from 15 to 29 % in less than 2 years [111]. Although open cystolithotomy is often used in cases of large or multiple stones, endoscopic management has gained popularity. Endoscopic therapy offers high stone removal rates and low complication rates [129]. The approach avoids an abdominal incision and entry into the peritoneal cavity and may obviate suprapubic tube placement in some patients [123]. However, endoscopy via the urethra or a channel carries the risk of damaging the urethra, catheterizable channel or BN repair when performed to treat a large stone. In addition, residual fragments left in the bladder after stone fragmentation can become a nidus for bladder stone recurrence. This risk may be decreased by using ultrasonic lithotripsy inside an endoscopically

introduced entrapment bag [78] or by removing calculi intact by an open or percutaneous approach. Previous attempts at comparing recurrence rates by surgical technique did not detect a statistically significant difference but were performed in small series (up to 31 patients) and did not account for method of stone fragmentation [67, 77]. In a recent study, Szymanski and colleagues found that bladder stones recurred in nearly half of patients within 9 years after first stone surgery, independent of treatment technique and patient characteristics [148].

Malignancy

Several case studies of bladder cancer developing after bladder augmentation have been published [7, 8, 21, 47, 55, 79, 106, 142, 156]. Soergel et al. reported transitional cell carcinoma in 3/260 patients with neuropathic bladder who had undergone bladder augmentation [142]. Tumors in gastric segment appear to occur more frequently and sooner after augmentation when compared to ileal segments [21, 156]. In a review of 153 augmented patients with a minimum of 10-year follow-up after augmentation, Husmann and Rathbun found a 4.5 % incidence of bladder cancer [62]. Patients with coexisting carcinogenic stimuli (prolonged smoking/chronic immunosuppression), or the inherent risk of malignancy as in bladder exstrophy, had a higher risk of cancer in their series.

A full review of this topic can be found in Chap. 11.

Perforation

The spontaneous perforation of an augmented bladder is an uncommon but very serious complication. The prevalence of spontaneous bladder perforation is reported between 6 and 13 % [11, 34, 48, 76, 94, 95, 135]. Perforation can result in peritonitis, sepsis, and death. The diagnosis may not be straightforward due to impaired sensation and varying levels of developmental disability in many people who have had an enterocystoplasty. Perforation may be due to traumatic catheterization, overdistension, chronic infection, ischemic necrosis of the intestinal segment, and increased intravesical pressure [5, 10, 30, 45, 125, 128]. Treatment usually requires emergent laparotomy, but conservative management has been successful in select cases. This approach has usually been reserved for patients without ventriculoperitoneal shunts [118]. In a review of 500 patients with augments, spontaneous bladder perforations were identified in 43 patients, for an overall risk of 8.6 %. The calculated risk was 0.0066 perforations per augmentation-year at risk. Approximately a third of the cases had perforated within 2 years of surgery, a third between 2 and 6 years postoperatively, and a third at more than 6 years after augmentation, highlighting the need for long-term follow-up. The use of sigmoid colon and bladder neck surgery were associated with an increased risk of perforation. The presence of a continent catheterizable channel was associated with decreased risk of perforation [94, 95].

Acid Base Disturbance

Due to the absorptive nature of bowel, metabolic changes may occur when enteric segments are introduced into the urinary tract. Given the small segments of bowel used, metabolic acidosis is rare in patients with normal renal function undergoing bladder augmentation [56, 96]. Hyperchloremic metabolic acidosis may result if ileal and/or colonic segments are used. When the ileum or the colon is exposed to urine ionized ammonium and chloride are reabsorbed. Ammonium absorption may also occur through substitution for sodium in the sodium–hydrogen antiport. The exchange of ammonium for a proton is coupled with the exchange of bicarbonate for chloride. Ionized ammonium may also be absorbed into the blood through potassium channels. Thus, bicarbonate and some potassium are lost [72]. Metabolic derangements may occur with the use of other enteric segment such as stomach or jejunum. Hypochloremic hypokalemic metabolic alkalosis may occur if gastric segments are used. The concentration of gastrin

seems to be important in this syndrome, as metabolic alkalosis becomes more severe with higher gastrin levels [149]. Though rare, when jejunum is used for urinary diversion, hyponatremic, hypochloremic, hyperkalemia, azotemia, and acidosis may develop [31]. Metabolic derangements are not isolated to augmented bladders and urinary reservoirs. Mild acidosis can be expected in up to 15 % of patients with an ileal conduit, of whom up to 10 % will require treatment [16, 22, 133].

Chronic acidosis may play a major role in the decrease in bone mineral density after bladder augmentation or urinary diversion. The majority of studies suggest that linear growth is not affected by bladder augmentation. Varying degrees of metabolic acidosis appear to resolve with no affect on linear growth [97]. However, prolonged acidosis could lead to osteomalacia and osteoporosis in adults [146]. In addition to the correction of the acidosis, dietary supplements with calcium, vitamin D and, in severe cases, bisphosphonates are recommended [115, 124, 138, 146].

In adulthood, progression of renal insufficiency teamed with worsening respiratory function (which can be restrictive airway disease, obstructive sleep apnea, and/or central apnea) can promote systemic acidosis. Baseline metabolic parameters should be carefully considered before any patient undergoes a surgery to change a patient from an incontinent, non-bowel-containing reservoir to a continent, bowel-containing reservoir because this may alter an important respiratory compensatory mechanism.

Vitamin B_{12} Deficiency

A reported sequelae of the use of ileum for enterocystoplasty is vitamin B_{12} (cobalamin) deficiency. A cobalamin concentration of 200 pg/mL is commonly regarded as the threshold below which supplementation should begin. The mechanism of the deficiency has been hypothesized to be secondary to removal of the distal ileum, which is the principal site of vitamin B_{12} absorption. Vitamin B_{12} plays an important role in DNA synthesis and neurological functions. While most deficiency is asymptomatic, it can result in megaloblastic macrocytic anemia and potentially irreversible neurological changes, such as peripheral neuropathy, loss of positional and vibration sense, balance difficulty and dementia [57, 87]. Reduction in serum B_{12} level may occur over a long period of time following ileocystoplasty and may require long-term serial vitamin B_{12} measurements [12]. Replacement may be parenteral or oral. Oral vitamin B_{12} replacement has been found to be well tolerated and highly effective in increasing serum levels to the normal range [152].

Attention to Conduit Urinary Diversions

Despite the popularity of bladder augmentation for those who have failed medical management, there are a myriad of surgeries performed with the goal of protecting the upper urinary tract from deterioration. These include sphincterotomy, detrusor injection of botulinum toxin, ileal chimney, and incontinent conduit diversion. In those with spinal cord injury, mortality from upper urinary tract disease after ileal conduit is historically reported at 25 % [28, 74, 102]. More recent studies show preservation of adequate renal function in almost all patients [25, 68].

People with MMC may be at increased risk of incisional and parastomal hernia. With long-term follow-up hernias may occur in up to 37 % of patients [66]. Risk factors for hernias include prior abdominal surgery, obesity, poor nutrition, chronic constipation, and poor abdominal musculature. Incisional hernias may include incarcerated viscera or enteric fistulization. Parastomal hernias are most common after ileal conduit/loop creation and may present with a poorly fitting stomal appliance or with bowel or urinary complaints [163]. Parastomal hernias are rarely encountered after catheterizable channels.

In addition to parastomal hernias, other complications of incontinent diversions include bleeding, skin irritation, prolapse, stenosis, ileoureteric anastomotic stricture, and retraction of stoma [25, 69, 74, 139]. Skin breakdown may be

related to poorly fitting appliances or retraction of the stoma. Stomal obstruction may lead to hydronephrosis, recurrent infections and/or renal failure from obstruction of the ileal conduit. Urinary tract infection may occur in up to 60 % of such patients [25, 68, 69, 139]. Pyocystis may also be encountered in those with a bladder left in situ. Periodic bladder irrigation, iatrogenic vesicovaginal fistula formation and cystectomy may become necessary when conservative methods fail. Marsupialization of the urethra and vagina in females as described by Spence with pyocystis may also prove effective and low risk for these patients [144]. Chronic metabolic acidosis has been reported in up to 20 % of patients after ileal conduit [73]. Renal, ureteral, and conduit calculi may occur in up to 40 % [69, 73, 74].

Attention to Mitrofanoff

The introduction of the catheterizable channel, whether utilizing the appendix or a channel constructed with tubularized ileum has significantly changed our approach to the care of neuropathic bladders [101, 103, 168]. Channels allow an alternative to catheterizing per urethra or, in the case of bladder neck reconstruction or closure, a substitute for the urethra. Placed in the lower abdomen or umbilicus, channels may increase independence or decrease the burden on caretakers, allowing the patient to be catheterized without transferring out of the wheelchair and removing clothes and undergarments.

Surgical revisions of catheterizable channels are not uncommon. With long-term follow-up in large series, up 39 % require revision [19, 82]. Complications may be relatively simple to correct as in stomal stenosis or may require extensive revision at a subfascial level due to channel incontinence, kinking, or angulation of the channel. Stomal stenosis rates as high as 50 % have been reported after long-term follow-up [82, 83]. Perforations and false passages may occur requiring creation of a new channel. Inflammatory or granulomatous polyps may occur due recurrent catheter trauma [43, 122]. These may be treated endoscopically [126]. It has been hypothesized that early complications are related to the healing process, and that the later complications are related to wear and tear of the conduits and changes in body habitus [82]. Based on a retrospective review of over 500 patients, Cain and colleagues found that Monti channels were two times more likely than an appendicovesicostomy to undergo subfascial revision overall. The spiral Monti to the umbilicus, in particular, was five times more likely than the appendicovesicostomy to undergo revision [19].

Sexuality and Sexual Function

Sexual function is a complex phenomenon involving desire, motivation, arousal, and orgasm. All aspects are poorly understood in adults with MMC. In a person with MMC, all or none of these may be affected. Sexuality in patients with congenital disabilities, including MMC may be affected for reasons including impaired self-esteem, dependence on caregivers, and lack of privacy [54]. Despite this, Hirayama and colleagues found 95 % and 100 % of male MMC and 83 % and 75 % of female MMC to have interest in the opposite sex and sexual desire, respectively [58]. In a study of 76 young adults with MMC, Lassmann and colleagues found that 24 % were sexually active. Sexual activity was not related to gender, degree of urinary incontinence, or extent of physical disability, but it was more likely in patients with lower level lesions. Interestingly, sexual function was not found to affect health-related quality of life in these patients [80]. In addition to the level of the lesion, hydrocephalus has also been found to affect negatively sexuality. Verhoef and colleagues found that sexually active patients were significantly less likely to have hydrocephalus [157].

The response to sensory stimulation and the ability to orgasm may be affected as the pudendal nerve (S2–4) is often compromised in MMC. A distinct neurological level that favors better sexual function has not been defined; however, lower

and less severe lesions are more favorable [33, 80]. In a study of young women with MMC, Roberts and Sawyer found 80 % of women with MMC had some genital sensation and 37 % of them had experienced orgasm [131]. Vulvar sensation and orgasm are rare in women with lesion at or above L2 [39].

Sexuality in men with MMC and normal cognitive development is similar to that of healthy peers, with 80–100 % reporting desire, fantasy, and interest in sexual activity [58, 130]. However, sexual activity in men with MMC is often delayed and more common in the subset of older men who live away from their parents [50]. Erectile dysfunction affects approximately 75 % of adult men with MMC and is most dependent upon the level of neurologic lesion. Sixty-four percent of men with a lesion at T10 or lower are reported to have erections compared to only 14 % with a higher lesion [40, 50]. In a study of 22 men with MMC, 95 % achieved erection by visual stimulation and in 86 % by tactile stimulation. However, only 27 % of the patients with erections were satisfied with penile rigidity. Ejaculation and orgasm was noted in 67 %. Orgasm was more frequently seen in patients whose external sphincter activity was maintained [58]. Ejaculation has been reported to be dripping in nature and may not be perceived as orgasmic due to absent penile sensation [15, 33]. Sildenafil has been reported to improve erectile function by 80 % in men compared to baseline and placebos, with 50 mg providing greater improvement when compared to 25 mg [110]. Recently, anastomosis of the dorsal nerve of the penis to the intact ipsilateral ilioinguinal has been described to improve penile sensation due to neural tube defects and low spinal cord lesions [64, 108].

In men actively attempting fatherhood, paternity rates are reported to be between 56 and 73 % and are more likely in men with L5 or sacral lesions [33, 81]. Despite high a rate of ED and infertility, normal testosterone production has been demonstrated in 90 % of men with MMC [33].

A more in-depth review of these issues, including special considerations for pregnant women with MMC, can be found in Chaps. 5.

Summary

- The following best practices are based on a review of the literature. To date, most studies are observational.
- As bladder function may change with aging and complications after reconstruction may occur into adulthood, lifelong, yearly urologic care is recommended.
- Urologic follow-up should include physical examination, renal ultrasonography, abdominal radiograph, and serum creatinine measurement.
- The use of routine urodynamics is controversial. The European Association of Urology Guidelines on Neurogenic Lower Urinary Tract Dysfunction recommends UDS every 1–2 years. However, UDS may be most useful if new symptoms, e.g., urinary incontinence, increased leakage between catheterization, changes in upper tract imaging, e.g., hydronephrosis and recurrent urinary tract infection, occur [155].
- In those with bladder augmentation, bladder substitution and urinary conduits, additional concerns include acid–base disturbances, vitamin B12 deficiency, calculi, malignancy, perforation, hernias, and obstruction.

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Approach to the Exstrophy Patient

3

Angela D. Gupta and John P. Gearhart

Presentation

Bladder exstrophy presents by prenatal ultrasound or at birth. It is a major birth defect that causes distortion of the lower abdominal wall and external genitalia. Exstrophy is thought to be on the spectrum of disease including epispadias, bladder exstrophy (both classic and variants), and cloacal exstrophy (EEC). Epispadias is the least severe form on the spectrum, presenting with a dorsally open urethra, mild pelvic diastasis, and a closed bladder. Classic bladder exstrophy (CBE) presents with a lower abdominal wall defect with an open bladder and a significant pubic diastasis. Cloacal exstrophy is the most severe end of the spectrum and presents with two bladder halves with the cecum in between. Cloacal exstrophy can present with other anomalies as well including gastrointestinal, central nervous system, and musculoskeletal.

The most common of these three is bladder exstrophy with a significantly lower incidence in the epispadias and cloacal exstrophy categories. Given that all of these are rare birth defects, the majority of published studies focus on bladder exstrophy. Therefore, much of the information presented when applied to other disorders in the spectrum will need to be tailored to the patient and the presenting disease. It is noteworthy that the live birth incidence is decreasing as improved, and earlier, prenatal diagnosis provides greater opportunities for elective terminations of effected fetuses.

Throughout childhood patients with EEC undergo multiple reconstructive operations with the goal of achieving urinary continence, adequate sexual function, and acceptable cosmesis. It is important to assess the integrity of the reconstruction, functional outcomes (urinary, sexual, psychological), and cosmesis in adult life.

Adults with exstrophy present either on routine follow-up, with an acute problem, or a specific concern. Herein, we will describe: initial evaluation routine, tailored follow-up, and known outcomes in the modern practice.

Evaluation

The initial evaluation of the adult exstrophy patient should start with a good surgical history and all accompanying records to assess what types of operations have been performed. The primary goals of exstrophy repair are to preserve renal function, establish urinary continence, and functional genitalia. There are many described reconstructions, and no standardization of the management of exstrophy [1–4], although

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outcomes have improved with time. The use of osteotomies and the timing of intervention in primary closures are also debated amongst the academic community [5, 6].

Renal Function

In the past, it was not uncommon that exstrophy patients experienced renal failure early in life, secondary to reflux and recurrent infections. The rates of renal dysfunction and scarring have been reported as high as 25 % in adults with exstrophy [7, 8]. In the modern era of exstrophy repair in regions near centers of excellence, most patients are closely followed and renal replacement therapy is a rarely needed and studies show minimal effect on renal function; however, it is important to continue to monitor renal function annually [9]. There remains no standard for follow-up of renal function, but most use routine serum creatinine and BUN as well as noninvasive imaging of the kidneys to follow renal function. A decrease in renal function may indicate reflux nephropathy, incomplete bladder/conduit/pouch emptying, or damage from repeat infections and should warrant a workup. This workup may include serum electrolytes, other methods of estimation of GFR, urodynamics, voiding cystourethrogram, and renal scanning when indicated.

Reconstruction

It is essential to understand the type and timing of operations that have been performed throughout the patient's lifetime. The exstrophy bladder is not the same as the normal bladder; therefore, it may not grow at the same rate as normal with age or have the same elastic properties that allow for low-pressure storage. As such, many of these individuals may require incorporation of a bowel segment to decrease intravesical storage pressures and increase capacity. After augmentation cystoplasty, renal deterioration can occur with normal bladder pressures secondary to a phenomenon described as volume-dependent obstruction, which is obstruction caused by exceeding a set volume in the bladder, which decreases the ability of the kidneys to drain [10].

Incorporation of bowel with bladder mucosa has been linked to increased risk of bladder cancer. Malignancy has been reported in the gastric portion of bladders augmented with stomach [11], which differs from small bowel and colon augmentation, where malignancy is traditionally not found on the bowel segment but in the bladder itself [12]. The etiology of malignancy in augmented bladders remains to be elucidated although these cancers typically present at a higher stage and have a shorter survival, when compared bladder cancers that occur in non-neurogenic and non-augmented cancers [11]. Studies suggest that the lifetime risk of malignancy in these patients is as high as 4.5 %; however, many have coexisting risk factors [13]. Adults with bladder exstrophy have a 17.5 % risk of developing a malignancy, which is about 700 times greater than the normal population [14]. There is no conclusive evidence that bladder augmentation or the use of a separate bowel segment into the urinary system is an independent risk factor for malignancy, as nonaugmented neurogenic bladders also demonstrate elevated risk of malignancy. Annual or biennial screening 10–15 years after augmentation with cystoscopy, urine cytology, and renal ultrasounds is recommended for these patients to detect early lesions and decrease the chance to presenting with advanced cancer [11]. Recent studies suggest that surveillance of these bowel segments in patients with congenital anomalies may be increasing the cost of health care without much benefit to these patients. The sensitivity of cytology is unknown in these bladders, while the specificity reaches 90 %. Endoscopy at times reveals abnormal findings, which rarely are pathologically significant [15]. The authors recommend screening with endoscopy.

Some patients require a not only a small patch of bowel used in the reconstruction but may have a diversion that is completely made from bowel, either large or small. The terminal ileum is the primary site of vitamin B12 absorption; therefore, it is important to test B12 levels in patients

where terminal ileum or large segments of bowel have been incorporated into a urinary reconstruction, 5 years after such a reconstruction.

Urinary Continence

One of the most important quality of life goals for the reconstruction of exstrophy patients is urinary continence. Many studies demonstrate continence rates as high as 90 % in patients with exstrophy [16, 17], although these studies come from centers of excellence in bladder exstrophy. In communities where specialized care of bladder exstrophy does not exist, this number is likely much smaller. Continent diversions can provide continence in most patients; however, these reconstructions require routine catheterization and are not preferred by children, adolescents, and parents [18]. Patients desire to achieve normal, spontaneous, and volitional voiding and avoid the use of catheters. The goal of bladder neck reconstruction is to emulate the normal sphincteric mechanism, which is disrupted in the exstrophy patient. Patient selection is key in bladder neck reconstructions. The most important selection criterion is a patient that desires continence. When the child starts to become aware, usually during school age years (5–7), that urinary incontinence is not normal and that others are not wearing pull-ups or diapers is the ideal time to start evaluating the child and also discussing the procedure with the patient. Any continence procedure should not be performed in patients who have not reached the emotional maturity or desire to achieve continence. Patients with high bladder capacities (almost normal per age), low post void residuals, and growing bladders are ideal for BNR procedure. The BNR takes away about 30 cm^3 of capacity at the time of the procedure—so it is important that the patient have a large enough bladder after to be able to store for at least 2–3 h without leakage. This procedure creates a fixed obstruction that the patient's bladder must overcome to empty; therefore, these patients must be motivated to empty regularly and strengthen pelvic floor muscles. Those that do not fit these criteria should be offered a continent diversion when they desire continence. Patients with failed previous closures and low bladder capacities have a lower chance of achieving continence with a bladder neck reconstruction; therefore, it is important to determine which patients are candidates for this procedure [16, 17, 19]. The ultimate result of the bladder neck reconstruction is to provide a constant level of resistance to the bladder outlet, which will allow for continence until the pressure of the fluid in the bladder exceeds that of the bladder outlet. The resistance of the bladder outlet however cannot exceed the detrusor pressure during voiding otherwise retention will result. Those that are not candidates for bladder neck reconstructions will need to pursue the continent diversion route when they are psychologically and socially ready.

Continence outcomes are reported in exstrophy patients however there is a lack of standardization in reporting, therefore making it difficult to compare outcomes between studies. In the majority of studies, continence is defined for the exstrophy patient as dry in between voids or catheterization at 3-h intervals [20]. Although high rates of continence are reported in the literature for exstrophy patients after reconstruction, most studies have short follow-up. Continence rates of 70 % in patients after successful primary repairs are reported at 5 years of follow-up; however, the remaining 30 % of patients either move on to continent diversions or continue to remain incontinent [21]. At five years of follow-up, 9 % of the patients had failed BNR and needed continent diversions. Longer-term outcomes remain to be elucidated for this group. Another study with a median follow-up of 12.5 years bladder neck reconstruction alone only yielded continence in 30 % of patients [22]. As the exstrophy population continues to be followed, it will be important to track their progress to understand the durability of continence and spontaneous voiding, nephrologic outcomes, and health-related quality of life measures in adult life.

Very few studies exist to understand what kinds of additional surgical interventions are

required throughout the lifetime of an exstrophy patient to maintain continence. These interventions may range from small adjustments to the bladder neck to as radical as a complete change in the method of continence. A high percentage of patients with exstrophy by adult life will need bladder augmentations and will use catheters to achieve adequate bladder capacity and preserve continence rates [23]. Changes in continence in this patient population may indicate a change in bladder compliance, detrusor overactivity, an infectious process, a failure of the reconstruction at the level of the bladder neck, or a failure of the continence valve for catheterizable stomas, hypercontinence, or the presence of a foreign body (stone, suture, etc.). It is, therefore, important to evaluate for a change in continence by history at least annually. If a change in continence is elicited, a thorough examination of the bladder and appropriate diagnostic testing is performed.

Sexual Function and Fertility

Sexual function, fertility, and satisfaction with genital appearance become of concern to the patient during puberty and remain thereafter. The genital reconstruction for males is more involved than for females. For men during the initial repair and during further reconstructions, the ejaculatory ducts, seminal vesicle, and vasa differentia are vulnerable to trauma and scarring. Damage to this area during reconstruction can result in anejaculation, low ejaculate volume, or retrograde ejaculation. Fifty percent of patients will have documented retrograde ejaculation and 20 % anejaculation, while 26.3 % have a low-volume ejaculation [24]. Patients that are diverted early in life, close to 75 % of them will experience azoospermia [25], which is significantly increased from the 19 % than those that are not diverted early in life [26]. The majority of patients that are diagnosed with azoospermia have ejaculatory tract obstruction when further studied, likely secondary to surgical manipulation. It can be difficult for these men to conceive naturally, and rates of natural paternity are very low (10–15 %) in these patients. When appropriate, semen sample should be obtained to determine if there is adequate sperm in the ejaculate. Many patients will be concerned in regard to their ability to conceive via naturally, before they desire paternity. It is reasonable to get semen analysis at this time; however, all patients should be counseled that conception can be achieved by assisted reproductive technology in all of these patients as there is no deficiency in spermatogenesis. Early referral to infertility centers is recommended for male patients with bladder exstrophy and abnormal semen analyses.

Rates of erectile function based on IIEF in these patients without the use of medications have been reported anywhere from 70 to 100 %. With the use of PDE5 inhibitors the rates of sexual function further increase; however, even with adequate erections only 50–60 % of patients are satisfied with erectile function. The most common reason for dissatisfaction is insufficient penile length and dorsal chordee [17, 23, 24]. Other studies paradoxically suggest reasonable rates of sexual satisfaction, with 60 % of men stating that they were completely satisfied with their sexual experience [23].

Females with exstrophy have less genital reconstruction than males. The vagina is short, has a more vertical lie, and often times an introitoplasty or vaginoplasty is required to start sexual intercourse and wear tampons. With intercourse exstrophy females can experience urine leakage, dyspareunia, lack of clitoral sensation, and pelvic organ prolapse [25], much of which may be secondary to previous surgical interventions. The pelvic floor musculature secondary to its formation has a larger urogenital hiatus allowing the pelvic organs more likely to prolapse. The majority of the levator ani muscle is also posterior to the rectum, leaving the anterior compartment with significantly less support. The anterior compartment contains the uterus, vagina, and bladder and the disproportionate support contributes to the incidence of pelvic organ prolapse in women with exstrophy [27]. On average, between 50 and 60 % of women with exstrophy will experience pelvic organ prolapse throughout their lifetime, requiring surgical intervention [28].

Fertility in women with bladder exstrophy is mildly impaired, but a normal reproductive course

is achieved in many patients [29]. A recent study demonstrates of those that are sexually active and desire pregnancy, about 68 % are successful. Only 20 % of women with bladder exstrophy will conceive naturally within one year of attempting conception, while the rest will either have delayed success or will require assisted reproduction. Regardless of whether women with BEE deliver via vaginal or caesarean section, they remain at higher risk of complications and should be cared for by high-risk obstetricians. Emergency caesarean sections result in a higher rate of complications including fetal mortality when compared to controlled caesarean delivery [30]. Over half of adult women with exstrophy will develop pelvic organ prolapse, and although pregnancy and introitoplasty is a risk factor about 30 % of women will have prolapse without pregnancy, secondary to the inherent lack of pelvic support in the exstrophy pelvis [28]. There is a chance of spontaneous abortion in secondary to pelvic organ prolapse in this population during pregnancy [29]. Women should be counseled appropriately regarding the higher risk of prolapse after pregnancy, and the likely need of surgical correction. Many surgical techniques have been described to fixate the uterus to the sacrum, which resolves the prolapse.

Special Considerations in Assessment and Care Planning

Patients born with exstrophy have a major birth defect that affects urinary continence, sexual function, and self-image. As such, they are more prone to psychosocial and emotional distress, secondary to multiple surgical interventions, hospitalizations, and outpatient visits throughout their lives. Sometimes, this results in trouble forming close emotional relationships with peers and sexual partners throughout adult life [32]. A multidisciplinary approach to the care of these children and their families is incredibly important from the very beginning and should persist into adult care. This should include physicians, specialty nurses, and psychologists to help set expectations for the families at the time of diagnosis and for the patient throughout his/her life [31]. Obviously, the requirement for multidisciplinary care does not end when childhood ends. Rather, many of the "adult urological issues" they face in fact become more relevant as they navigate adulthood. For this reason and for the poorly described but widely accepted changes to continence and bladder function that occur after childhood, transition to an adult urological care team is imperative after these patients age out of pediatric care.

Conclusion

In adult life, it is critical that patients affected by BEE be followed clinically. This includes annual assessment of renal function and bladder function as well as screening for sexual dysfunction, fertility services, and age-related urological deterioration (pelvic organ prolapse, etc.) During adult follow-up, it is important to address the patient in a holistic manner addressing all of these aspects. A seamless transition in their care and continued emotional and psychological support, with appropriate medical care will help these socialize more easily.

Summary

Adult patients with BEEC should be evaluated annually with a complete physical exam, including pelvic exam for women and assessment for the following:

- Renal function: renal ultrasound, serum creatinine, or GFR measurements
- Bladder cancer risk assessment: frequency of UTIs, hematuria, bladder pain, transplant status, and other risk factors.
- Urinary continence status: method of bladder emptying; changes in urinary continence since prior visit, satisfaction with continence
- Sexual function: desire, erectile/ejaculatory function (men), dyspareunia/anorgasmia (women), satisfaction with

sexual function, and fertility considerations/concerns
- Nutrition: Serum chemistry, vitamin B12 levels if appropriate
- Psychological health: counseling if appropriate or if desired.

Additional diagnostic imaging, including KUB, cross-sectional imaging, cystourethrogram, urodynamics, and cystourethroscopy may be warranted every 1–3 years, depending on functional status, development of new symptoms, and prior reconstructive history.

BEEC patients should be followed by a urologist or pediatric urologist who feels comfortable with major reconstructive surgery and the long-term complications that may need intervention. In addition, a multidisciplinary team including one or more of the following specialties should be considered as patient history and needs direct:
- Nephrology
- Psychiatry/psychology
- Internal medicine
- Gynecology (women)
  Orthopedics or physical medicine

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Approach to the Adult Hypospadias Patient

4

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Introduction

The aim of the surgeon in repairing a child's hypospadias is to create a straight penis, a neourethra of adequate caliber, a meatus at or near the tip of the glans penis, and normal voiding and good penile cosmesis with minimal complications. Modern techniques report an almost 90 % success rate but often have short-term follow-up. A successful repair in children is often judged by the cosmetic result and the quality of micturition. However, some urethroplasties deteriorate from childhood to adolescence. The high success rates often cited for various techniques are virtually impossible to report with certainty considering the fact that late stage failures are well documented and reported in the literature. A three-decade series from 1978 to 2009 by Prat et al. [1] found 4.6 % of 820 patients required further revision in adolescence. A recent population-based study on more than 5,000 patients found a 9 % secondary surgery rate for distal hypospadias repair ($n = 3{,}553$) and 32.2 % ($n = 423$) for proximal hypospadias repairs. Secondary surgery was also more common in children presenting at an older age [2].

The degree of hypospadias and the type of repair utilized factored into the outcomes. In severe hypospadias, there is often proximal division of the corpus spongiosum and significant chordee. Achieving good long-term results for proximal hypospadias is far more challenging than for distal hypospadias. The definition of a successful outcome has changed over time. In the past, success was defined as a subterminal coronal meatus without chordee. Hinderer et al. [3] stated confidently that the long-term outcome of a hypospadias repair can be predicted only after 2 years of follow-up. Johansson and Avellan [4] reported favorably on the long-term results of Denis Brown, a technique that is currently obsolete. These reviews suggest that short-term patient satisfaction may extrapolate to comparable long-term outcome, although follow-up studies after sexual maturity has occurred are very limited and criteria for "success" have yet to be defined. As techniques have improved more literature has been published on psychosocial, micturition, ejaculation, and cosmetic outcomes. Some of these reports include functional and anatomical complications as well as perceived poor cosmesis with a desire for further surgical correction to look more normal. Bracka outlined the importance of the patient's own satisfaction in the cosmetic appearance of the penis. In a long-term survey, 40 % of his patients requested surgical revision [5]. The Cleveland Clinic experience [6] reported that the most

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Table 4.1 Adult and adolescent hypospadias repair 1980–2011 (18–39 year olds)

Presenting complaint	*N*
Chordee (11 fistula)	41
Urethral stricture + chordee or fistula	35
Lichen Sclerosis (LS)	11
Hairy urethra (stones or retention)	8
Spraying of urine/subterminal meatus	57
Aesthetic concerns ± spraying	59
Primary repair (6 distal, 4 mid-penile)	10
Total	221

Personal experience

common presenting complaints were voiding symptoms including dysuria, spraying, urgency, and urethrocutaneous fistula.

Hypospadias repair in adults can be divided into three groups: the first group are primary cases, the second group include patients who have had a previous repair during childhood and present with a complication, e.g., urethrocutaneous fistula, persistent curvature, urethral stricture, urethral diverticulum, and poor cosmesis and the third group are patients who have undergone several failed surgeries and previously referred to as "hypospadias cripples." Failed multiple attempts at hypospadias repair often leaves the patient with a penis that is scarred, hypovascular, and shortened. In many patients, the type of repair as well as the number of surgeries that were done in childhood is not known. Frequently, the local tissues cannot be used to assist in the repair and extragenital sources must be utilized. Herein, we describe the issues surrounding the adult hypospadias patient and the management from our experience (Table 4.1) and the literature.

History

Perhaps no other surgical condition in pediatric urology has inspired more surgical innovations than hypospadias. There are more than 200 surgeries that have been described for hypospadias correction and a recent Medline search revealed more than 5,000 publications on the subject. There is nothing new in hypospadias surgery that has not been previously described. As with any surgical procedure, the results we see today are directly attributable to the building process in medicine, capitalizing on other ideas, refining them and adding subtle improvements to end up with a surgical technique that is reliable and reproducible by other surgeons.

The significance of chordee was appreciated by Galen in the second century AD and forgotten until Mettauer [7] in 1842 recognized skin shortening as a cause of chordee. It was not rediscovered until 1967 by D.R. Smith [8] and 1970 by Lowell King [9] who reemphasized that the principal structure of the penile curvature is commonly proximal to the meatal orifice, a concept described by Mettauer more than 100 years prior when he advocated "a succession of subcutaneous incisions until the organ is liberated" [7].

In 1869, Professor C. Thiersch [10] reported that in 1857 and 1858 he tubularized the urethral plate in a child born with epispadias and credited the technique to August Brauser, his one-time assistant. Thiersch's classic article illustrated the design of the flaps and the asymmetric lateral incisions so that the suture lines are unopposed. In 1874, Duplay [11] described the tubularization of the urethral plate distal to the hypospadic meatus. He also stressed the importance of complete chordee release before urethroplasty.

In prior years, glandular and coronal hypospadias were often not repaired because the complications overshadowed the benefits of surgical correction. Duckett's [12] meatal advancement and glanduloplasty technique (MAGPI) was designed to reduce the risks of formal urethroplasty in distal hypospadias. Zaontz [13] applied the Thiersch–Duplay principle to the repair of distal hypospadias. He reported excellent results with the glans approximation procedure (GAP), an operation indicated for patients with coronal meatus and a deep glandular groove. This procedure can be used in adults with equal success. Midline incision of the urethral plate was first reported by Reddy in 1975 [14]. He made the incision to excise the "fibrous tissue" in the midline that he believed to be the cause of chordee. He then combined the incision with the Thiersch–Duplay method and tabularized the urethral plate. Rich et al. [15] incised the plate to create a normal

slit-like meatus by hinging the distal urethral plate longitudinally in the midline, but Snodgrass [16] reported and popularized the tubularized incised plate urethroplasty (TIP) repair which is currently the most widely used technique.

Epidemiology

Hypospadias is the most common urogenital malformation second only to cryptorchidism and occurs in 1/250–300 [17, 18]. It has been previously postulated that the incidence of hypospadias in children is rising [19]; however, subsequent studies have not shown the same results [20]. Hypospadias has been associated with advanced maternal age [21, 22] and in vitro fertilization [23].

Given the dearth of longitudinal literature on hypospadiacs, little is known about the natural history of this population. While it is well documented that hypospadias patients—both previously repaired and never-repaired, frequently present with urinary complications in adolescence and adulthood [6, 24], the "hypospadias cripple" presents the greatest surgical challenge and these patients are subject to the highest complication rates [25]. The incidence of late complications is uncharacterized, with some studies reporting about 50 % of patients experiencing some complications. While about 1/3 of these complications occur in the first 5 years, nearly 1/5 of the complications occur after 5 years [26]. Importantly, this study did not include patients who underwent staged reconstructions, and therefore, this cohort represents a group of patients with "mild to moderate" defects. Complications can come in the form of cosmetic issues, chordee, fistula/diverticulae, foreign material in the urethra (typically hair/stone), and recurrent stricture. Surgical therapy therefore must be tailored to the complication and a detailed discussion of all these problems is beyond the scope of this project.

Long-Term Outcomes: Psychosocial, Erections, Ejaculation, Micturition (Figs. 4.1, 4.2, 4.3, and 4.4)

Questions on the long-term adjustment of patients have now become de rigueur and a number of validated study questionnaires have been developed to follow these patients into adolescence and adulthood to assess the quality of repair and perhaps illustrate the importance of continued follow-up. Unfortunately, not all studies use validated questionnaires and therefore comparing results is problematic. As evidenced by the increasing literature on hypospadias failures presenting in adulthood, hypospadias in childhood has the potential to produce long lasting effects well into adulthood.

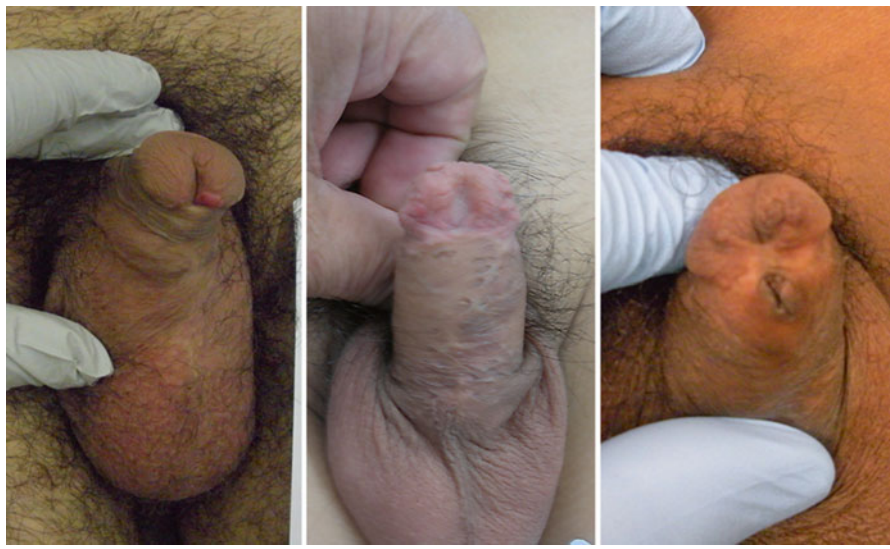

Fig. 4.1 116/221 adults complain of spraying from subterminal meatus and poor aesthetics

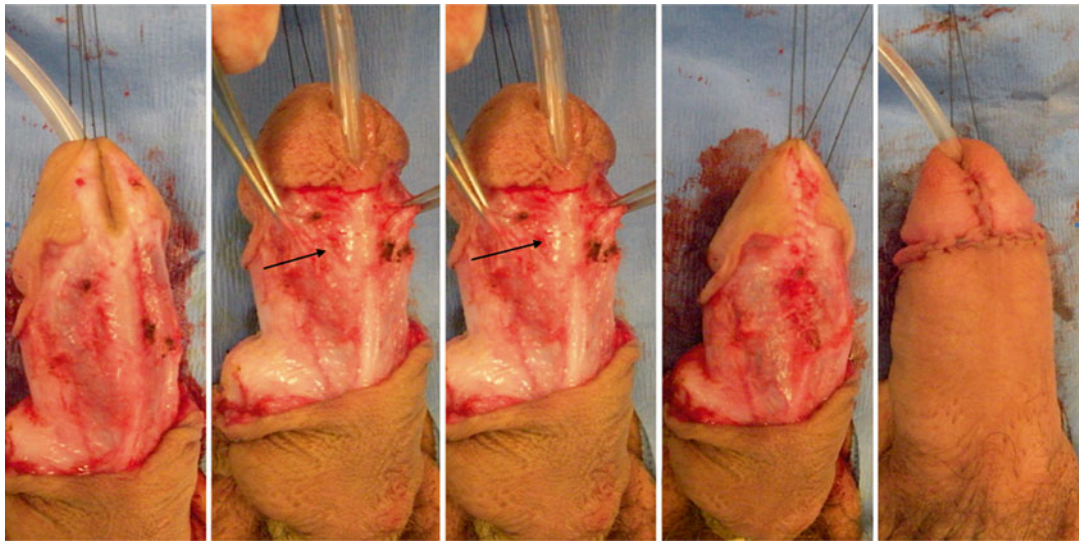

Fig. 4.2 Urinary spraying, subterminal wide meatus and spongiosum deficiency (*arrow*). GAP repair and spongiosal approximation to prevent diverticulum formation

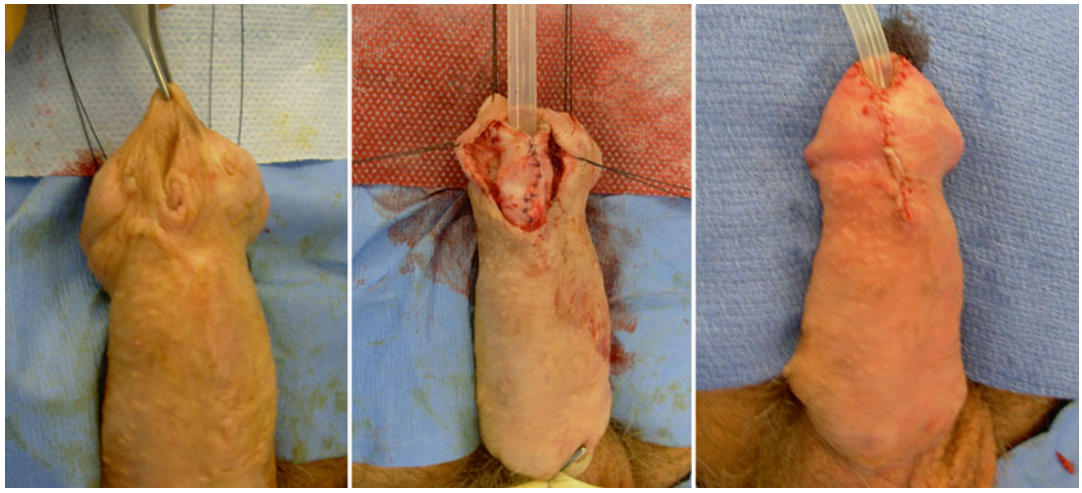

Fig. 4.3 Distal urethroplasty and glandular sculpting for urine spraying and cosmesis

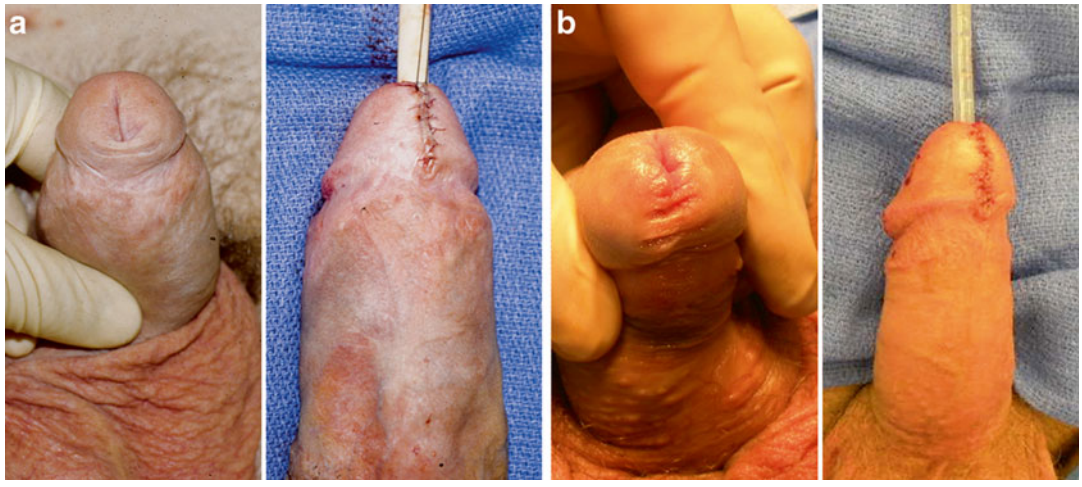

Fig. 4.4 (**a**) Urine spraying: GAP repair. (**b**) Suture tracts: glans sculpting

When reviewing studies on long-term patient-centered outcomes, it is important to consider the timeline in which the repairs were performed. Older techniques have historically worse outcomes and have fallen out of favor, influencing the reported outcomes. Adults and adolescents with subterminal or irregular meatus who had proximal hypospadias repaired during childhood often complain of spraying and angulation of their urinary stream. These patients also commonly note post-void dribbling of urine and the need to milk the ejaculate as the seminal fluid stagnates in the neourethra which lacks spongiosum tissue. In our experience, 116/221 (52.4 %) adolescents and adults with previous hypospadias repair complained of urine spraying and aesthetic concerns. They reported more sexual dissatisfaction as well as dissatisfaction with penile appearance. However, the majority had no difficulty with sexual intercourse except in patients with significant curvature.

In 1989, Bracka published a long-term follow-up of 213 patients with a history hypospadias in childhood of whom 196 had undergone surgery [27]. This landmark study followed patients with questionnaires and physical examinations for those who had a "meatal ventralizing or terminalizing repair" of hypospadias. Patients were assessed for location of meatus, urinary dysfunction, appearance, penile size, sexual behavior and performance adequacy of follow-up and guidance. The impetus for review was based on older reports that patients did not need long-term follow-up after hypospadias repair. The number of procedures required for repair varied from 3.6 to 7.2 with higher numbers in those with "short urethra" and proximal hypospadias. On review, many of the patients had a sub-glandular meatus, which Bracka theorized was due to retraction during growth. Not surprisingly, these patients also reported more spraying on the questionnaire. 38 % of patients reported feeling deformed and 72 % felt appearance was just as important as function. When asked about understanding of their condition, a surprising 60 % had never heard of hypospadias and the Bracka postulated that ignorance of their condition caused further social anxiety. In fact, on further review 44 % of patients requested further surgery for dissatisfaction with stream, appearance, residual curvature, or stricture. In 181 patients who had reached sexual maturity, 1/3 felt inadequate about the size of the penis and in those who underwent proximal hypospadias repair penile length was shorter in flaccid, stretched and erect position compared to the more distal repairs. While 77 % reported having had satisfactory sexual intercourse, ejaculatory complaints predominated with 33 % of patients reporting dribbling ejaculation and 4 % dry ejaculate.

Mureau et al. [28] reported outcomes in 116 patients who underwent hypospadias repair between 1960 and 1992 at two different hospitals. The patients were compared to a group of 88 controls who had undergone inguinal hernia repair. A semistructured interview was performed in boys with an average age of 14.4 years vs. 13.9 years for controls. Patients with hypospadias were more likely to have anxiety and inhibition in seeking sexual contact and 25 % were dissatisfied with penile appearance. The severity of hypospadias or number of surgical procedures did not seem to differ between the groups. However, 19 % of patients in whom surgery was performed after 6 years of age were less satisfied with the surgical result and had a worse genital view than the younger children. Older boys at the time of study (13–18 years) were less satisfied with appearance than their younger counterparts (9–12 years), 31.6 % vs. 13.2 %, respectively. Overall, 39 % patients expressed desire for further correction. The importance of early hypospadias surgery was reiterated by Jones et al. [29] who demonstrated that using validated questionnaire, Hypospadias Objective Scoring Evaluation (HOSE) 80 % of patients had excellent surgical outcome. They concluded that when surgery was completed before age 5 years, boys had no preoperative memories. An association was found between no recollection of surgery and satisfaction with body appearance. The HOSE scheme comprises five domains including meatal location, meatal shape, urinary stream, curvature at erection and fistula.

In a recent study, Chertin et al. [30] reported objective and subjective sexual outcomes in 119 adult patients (older than 18 years) who had their

hypospadias repair performed in childhood between 1978 and 1993. In addition to the Index of Erectile Function (IIEF), they used an invalidated questionnaire of patient perception of psychological well-being and penile appearance. Patients were divided into three groups based on the location of the original meatus: group 1 included 45 patients with glandular hypospadias, group 2 consisted of 56 with distal hypospadias and group 3 included 18 patients with proximal hypospadias. Multiple techniques were used at the time of initial repair. Almost all patients who had glandular and distal hypospadias were satisfied with penile appearance whereas only 11 % in the proximal group were pleased. Mild erectile dysfunction was reported in 50 and 72.2 % in those with distal and proximal hypospadias, respectively; however, 16.7 % of the proximal hypospadias group reported moderate erectile dysfunction. Premature ejaculation was common, reported to be present in 88 %. Additionally, more patients with proximal hypospadias reported decreased sexual quality of life compared with the distal and glanular hypospadias groups.

Long-term outcomes in patients with a history of proximal hypospadias are scarce. Lam et al. [31] performed two-stage hypospadias repair in 44 boys with severe hypospadias and chordee. The average age at response was 15.6 years. The surgeons reported all patients had a satisfactory physical examination However, ten patients reported minor urine spraying, ten had to milk the urethra to completely eliminate, seven complained of minor post-void dribbling and five others complained of pain or a weak stream. Of the 20 patients who reported ejaculation, 9 had to milk the urethra Aulagne et al. [32] also reported outcomes in severe hypospadias in 27 patients (age 20–35) all of whom had associated chordee. Various surgical techniques were used. In addition to non-validated questionnaires, the authors used the Hypospadias Objective Scoring evaluation (HOSE) questionnaire. Additional repairs not named included scrotal and penile skin flaps. Micturition was evaluated, and only 15 % of patients had no urinary symptoms. Almost half the patients experienced dribbling. None of the patients reported problems with erection while 11.1 % reported retrograde ejaculation. Cosmesis was noted to be slightly abnormal by 51.9 % patients while 22.2 % felt it was considerably different. Five patients reported slight to moderate curvature.

Mondaini et al. [33] performed a cross-sectional analysis of men with hypospadias and compared them to 500 controls. Men with hypospadias were less likely to initiate sexual contact, especially if they had more operations. Only 16.6 % had sexual intercourse compared to 42 % of controls; however, all reported satisfaction with the experience. More patients reported poor genital appearance (26.1 % vs. 2 %) compared to controls as well.

In a comprehensive review of the literature, Rynja et al. [34] performed a meta-analysis and reviewed general results, micturition, uroflowmetry, cosmesis, sexuality, and relationships. They included 20 studies with 1,069 patients and reported outcomes compared to controls if included in the original study. The authors also evaluated patients with severe hypospadias. Mean age at follow-up was 27 years (14.0–34.7) and the patients had an average of 2.7 operations. There were 742 subjects in the control group. Patients with hypospadias were more likely to complain of lower urinary tract symptoms including spraying and dribbling (>50 % of the time). Uroflowmetry revealed lower Q_{max} compared to controls (5–39 mL/s vs. 11.9–64.6 mL/s) but mean Q max did not differ.

Patients with severe hypospadias were significantly less satisfied with penile appearance compared to other hypospadias patients and controls, although overall 33.5 and 35.4 % of hypospadias patients and controls, respectively, felt their penis was abnormal compared to their peers.

It is important to note that surgeon perception may be different than patient perception regarding successful outcome. Mureau et al. [35] found overall patients were less satisfied compared to the surgeon with overall genital perception including glandular size and shape, penile thickness, flaccid penile size and appearance of scrotum and testes. After physical exam 11 % of boys

went onto further surgery due to fistula, curvature, and location of meatus, findings that did not prompt them to seek out surgery before the office visit. This study highlights the importance of patient-reported outcomes in long-term studies related to penile surgery.

Conclusions

Body image development occurs in stages and puberty stands out as a particularly sensitive time as the teenager undergoes major changes in his physical appearance. Adolescents become more self-aware and develop the capacity for self-reflection and sexual experience. They depend heavily on what others think and respond with complex emotional reactions. There is significant pressure to conform to normality in the present image-conscious society. Hypospadias patients may have more negative genital appraisal and anticipated ridicule by a partner [28]. A significant number of the adults born with proximal hypospadias encounter micturitional, ejaculatory, and psych-sexual difficulties.

The majority of adults born with distal hypospadias corrected by a modern well-executed "terminalizing" technique are satisfied with their genital appearance. However, long-term outcomes for the modern procedures of the twenty-first century remain to be elucidated in the future.

For primary hypospadias repair, a near-perfect functional and aesthetic result represents a successful outcome and is indeed achievable for many using modern techniques. However, for the minority who require multiple surgeries, which compromised the quality of the genital tissues, the outcome can be severely disabling and the patient is required to accept a lower standard for success. For example, a patient who has endured multiple surgical failures is happy to void through a subterminal or even a coronal meatus, but such an outcome would be unacceptable in a primary repair of a "virgin" hypospadias. Progress in hypospadias surgery will require long-term patient-reported outcome studies to better determine how the patients fare in adolescence and adult life.

Summary

The aim of the surgeon in repairing a child's hypospadias is to create a straight penis, a neourethra of adequate caliber, a meatus at or near the tip of the glans penis, normal voiding, and good penile cosmesis with minimal complications.

Hypospadias repair in adults can be divided into three groups:

- Primary cases
- Patients who have had a previous repair during childhood and present with a delayed complication in adulthood
- Several prior failed repairs ("hypospadias cripples")

Rates of secondary surgery for hypospadias are not entirely characterized, but studies suggest:

- 9 % secondary surgery rate for distal hypospadias repair
- 32 % for proximal hypospadias repairs

Problems encountered in postpubertal life include:

1. Urinary—spray, deviated stream, weak stream, dribbling
2. Sexual—erectile dysfunction, ejaculatory dysfunction
3. Infertility
4. Cosmesis—scarring, persistent chordee
5. Psychosocial—sexual inhibition, dissatisfaction with appearance, overall decreased QoL

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Part II

Sexual Function, Fertility, Genital Function

Sexual Function and Pregnancy in the Female Myelodysplasia Patient

5

John C. Thomas, Amanda N. Squiers, and Melissa R. Kaufman

Introduction

Treatment of the urologic sequela of myelomeningocele (MMC) in children is an exceedingly complex endeavor. Remarkable technical progress in the past several decades has resulted in between 50 and 94 % of these MMC patients once destined for death to survive to adulthood [1]. Indeed, due to a combination of decreasing incidence due to vigilant prenatal prophylaxis as well as comprehensive urologic care for patients with MMC to protect renal function, the tide has shifted and the majority of contemporary MMC patients are actually adults. Yet very few mechanisms exist to insure a continuity of care for this unique population, particularly with regard to sexual function and fertility. The protean issues revolving around the topics of sexuality and reproduction in female MMC patients progressing to adulthood presents a constellation of challenges for the adult urologist managing their care. Herein, we will discuss some of the critical considerations and barriers for counseling and management of the female MMC patient with regard to sexuality and reproduction.

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For many of the young men and women transitioning to adult care, issues regarding sexual and reproductive health are unsurprisingly of increasing importance. Often the first adult clinic visit to urology presents the primary opportunity for many of these patients to begin to explore these matters of substantial social consequence. Unfortunately, reports suggest that for the MMC population, only a small percentage described discussing sexuality issues with a physician [2]. A combination of unfamiliarity with available literature, a dearth of well-designed studies to help guide evidence-based counseling, and distinctive, highly individualized situations often result in management dilemmas for physicians and patients alike. Documented experience, particularly with regard to recommendations regarding pregnancy, is often anecdotal and based on small case reports or consensus opinion of experienced surgeons.

Tremendous barriers exist for MMC with regard to providing standard diagnostics and treatments for urologic care due to the vast array of potential pathophysiologic issues. Evolution of our counseling for the MMC population will most certainly expand in the coming decades as more of these patients survive to adulthood with functional capacity to embark on sexual activity and pregnancy. Herein, we review available literature regarding practical considerations for counseling and management female patients with MMC desiring pregnancy, particularly those following genitourinary reconstruction.

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Sexual Function

Initial assessments of the MMC population regarding sexual function were fundamentally focused on neuroanatomy and loss of sensory capabilities [3–6]. Recapitulating the societal bias driving abundant research in normal male versus female sexual function, a similar differential emphasis appears regarding studies in MMC females. Even as the field of normal female sexual dysfunction evolves, are analogous outcome measures such as desire, lubrication, and orgasm directly adaptable in the MMC population?

Vertebral column abnormalities may manifest in an array of sensory and motor deficits and resultant sexual dysfunctions theoretically correlate to the level of the spinal defect [3, 6]. In general, patients with MMC can be divided into three groups defined by motor level: (1) lesions at or above L2 (essentially all wheelchair bound patients); (2) lesions between L3 and L5 (patients may ambulate with braces/aids/surgical procedures); and (3) lesions at or below S1. Still, since the defect in the developmental pathway is unique in every patient, the ultimate sensory and motor manifestations, as well as cognitive and emotional development relating to sexual function, must be assessed individually. Females with MMC most frequently display normal genital and reproductive anatomy, but may be short for their age, wheelchair bound, and restricted by muscular deformities such as kyphoscoliosis [5].

However variable the manifestations of MMC lesion level, commonly patients with deficits at or below S1 display minimal neurologic defects and may display near normal sexual function [4]. However, some authors have suggested that even for higher level lesions, clinical experience reveals the absence of genital sensation does not preclude sexual satisfaction and therefore alternative sensory pathways may dominate [5]. One important consideration occurs in patients with autonomic dysreflexia as orgasm may result in painful contractions or incontinence depending on the level of bladder filling [7]. Additionally, lack of vascular engorgement in MMC patients due to defects in the parasympathetic pathway may predispose to issues with vaginal secretions during intercourse which would benefit from usage of soluble lubricants.

An often inconspicuous factor which the practitioner is obligated to address revolves around the psychosocial impairments frequently existent in the MMC population [8]. The process of normal adolescent development and sexual maturation may be exceedingly complex in this population due to a variety of factors. Socialization with peers, a dominant factor in the development of successful sexual relationships, may be a particular hardship for many female patients with MMC [8]. Interestingly, lesion level does not appear to affect the ability of the MMC patient to form relationships [9]. Prominent risk factors contributing to characteristic delayed social development may include actual cognitive handicap, poor manual dexterity, lack of educational opportunities regarding psychosexual issues, and a dominant parental influence [5]. Due to the intricacies of the caretaker/parent relationship that may have evolved with the disabled patient, there appears to be a discernible absence of the normal adolescent–parent conflict in MMC patients [10]. This conflict is essential to developmentally shift the adolescent away from the parent-centered to the peer-centered relationship. Factors that promote defiance during young adulthood may be magnified for MMC adolescents and negatively impact patient compliance.

Concerns of fertility and sexuality may arise prior to the capacity to transition to an adult provider. Indeed, the female MMC patient is prone to precocious puberty with many patients undergoing menarche at as early as ages 6–9 [5, 11]. The comorbid deficits in the hypothalamic–pituitary–gonadal axis, particularly in individuals with hydrocephalus are understood to contribute to development of premature sexual characteristics which the family and patient are often poorly prepared to address [12]. Mobility impairments may produce difficulties with hygiene, further impacting evolving body image concerns [13]. Delayed psychosocial development, impaired executive function teamed with premature physiological development leads to even more widening of the gulf between physiological readiness and psychological

readiness with respect to sexual function. Patient education, including the use of latex-free barrier contraception, remains an important role of the urological health care provider in minimizing risk during this vulnerable period.

After preservation of renal function, continence remains a primary goal for management of both the pediatric and adult MMC patient. Continence becomes an increasing social issue with aging and the development of a woman's sexual identity. Numerous studies have underscored this relationship demonstrating a principal barrier to development of intimate relationships for the MMC population is concern for incontinence [2, 14]. Additional questionnaire-based evaluations have confirmed that a key predictor for the MMC patient's capacity to find a partner and engage in sexual activity was lesion level, favoring those with lower lesions [9]. One critical influence in assessing predictors of sexual partnering was the presence of hydrocephalus which appears to significantly diminish socialization capacity and associated sexual functioning [15].

Sex Education

Of key concern for the transition practitioner involves building expectations with the individual MMC patient, creating an environment of independence, and promoting patient self-management and confidence. Discussion of sexual development topics are certain to be complex, particularly in situations of high-level parental involvement, but must be accommodated to appropriately propel transition to adult-centered care for this vulnerable population.

Contemporary studies investigating levels of sex education and exploring desires for partnering and pregnancy in women with MMC have revealed the majority of young adults with MMC have had sexual experiences and have similar desires with regard to relationships, sexuality, and pregnancy as their normative counterparts [15–17]. In a questionnaire-based survey of MMC patients and their parents, 95 % of patients indicated inadequate knowledge about sexual and reproductive health relating to MMC and 59 % of parents considered they had inadequate knowledge [2]. Not surprisingly for a population primarily managed by pediatric specialists, only 39 % of patients had discussed sexuality issues including fertility, heredity, pregnancy, and contraception with a physician. In an Italian population of almost 300 MMC patients, alarmingly only 5 % of female patients actually discussed sexuality with a health care provider [9].

Not surprisingly, 93 % of MMC adolescents and 100 % of parents reported they would categorically discuss reproductive issues if the dialogue was initiated by their doctor. Although somewhat lower than age-matched controls, a significant degree of sexual intimacy was reported for MMC patients, with 60 % reporting an intimate relationship, and 25 % reporting sexual intercourse [2].

Overall, increasing awareness must squarely rest on the treating practitioner and discussion of sexual and reproductive subjects should be integrated into patient counseling. Nearly, all reports in the literature demonstrate a discrepancy between sexual desire and activity in the MMC population demonstrating that many patients may enjoy dramatic quality of life enhancement when appropriately counseled.

Latex Allergy

Pediatric urologists are intimately familiar with the incidence and risks of latex allergies in the MMC population which have been estimated to approach an incidence of 60 % [18]. Although most urologists and obstetrician/gynecologists may be accustomed with and prepared for the intraoperative consequences of a latex allergic reaction, special considerations may be necessary when counseling patients regarding sexuality and birth control [19]. Primarily, patients must be cognizant to utilize latex-free condoms, sexual aids, and intrauterine devices [20]. Of additional concern with intrauterine devices is the potential amplified risk for pelvic infection. For the immobile patient, use of estrogen/progestin contraceptives may also escalate risk for thrombotic events [21–23].

Preconception counseling is strongly encouraged when the opportunity exists and the pregnancy is planned. Involvement of a multidisciplinary team with high-risk obstetrics, reconstructive urology, anesthesiology, orthopedics, and neurosurgery should be considered for consensus decision-making for the MMC female desiring pregnancy. Provision for social work counseling may furthermore be valuable. Genetic components of neural tube defects must be clearly delineated for MMC patients desiring conception. Risk of transmission to offspring if one parent is afflicted with MMC is variably quoted at 1–8 % [24–26]. The threat is identical if the affected parent is male or female; however, the incidence in female offspring is 1 in 13 and diminishes to 1 in 50 for male children. However, if both parents are affected, the neural tube defect transmission rate increases dramatically to 15 %.

Since polymorphisms in the folic acid metabolism pathway are considered primary deficits in the development of neural tube defects, promotion of folic acid supplementation for women desiring pregnancy is of critical importance [27]. By the early 1990s, a substantial public health effort was initiated in the United States through the collaboration of the Centers for Disease Control, Health Services Administration, Food and Drug Administration, and the National Institutes of Health [28]. This program involved a three-stage approach for the prevention of neural tube defects: (1) dietary supplementation of 0.4 mg of folic acid for low-risk women and 4 mg of folic acid for high-risk women of childbearing age; (2) improvements in dietary habits; and (3) fortification of the US food supply. Notably, compared to routine supplementation of women without MMC of 0.4 mg folic acid per day, doses of 4–5 mg per day have been advocated for the MMC patient desirous of fertility [5, 28]. Prophylaxis is currently recommended with folic acid supplementation for 3 months prior to pregnancy and continuing through week 12. Despite this regime, there remains a risk for development of MMC due to inborn errors of metabolism or discrepancies in the absorption of folic acid products [29]. Additional genetic, dietary and epigenetic alterations responsible for these continued hazards for development of neural tube defects are topics of vigorous current research initiatives in the post-folate supplementation era.

Monitoring and counseling of progeny for neural tube defects should be employed and tailored to the individual desires of the parents [30]. Prenatal diagnosis of neural tube defects has been incorporated into routine prenatal care via screening. Screening prior to 20 weeks is now standard with the use of serum testing, high resolution ultrasound and chorionic villous sampling, providing earlier diagnosis and greater opportunities for elective termination if the parent(s) desire that option. Fetal magnetic resonance imaging (MRI) may also serve as an adjunct imaging modality with ultrasound to improve prognostic prediction.

Fertility

In general, females with MMC are considered to have normal fertility with up to 70 % of those who conceive having successful pregnancies [19]. However, as discussed in further detail below, the gravid uterus may impact already tenuous balance and ambulation issues, ventriculoperitoneal (VP) shunt drainage, bowel and bladder function, urinary diversion function, skin integrity, pulmonary function, cardiac function, and foremost, urinary infection risk.

For patients who have previously undergone extensive pelvic surgery, experienced authors have suggested that visceral adhesions may negatively affect fertility due to uterine retroflexion and concomitant issues with conception and implantation [31].

General Considerations in Pregnancy

Each woman with MMC presents a unique challenge for the practitioner. The myriad considerations include the patient age, underlying comorbid disease, genetic implications for the offspring, pelvic bony and muscular anatomy, obesity, urinary diversion status, prior abdominal surgeries, renal function, presentation of the fetus,

and even considerations for care of the infant. Appreciation of these physiologic, anatomic, and social considerations should guide the physician to optimize organization of multidisciplinary care for these women.

With regard to urinary diversion, pregnancies for MMC patients most often follow reconstruction by many years. Initial goals of urinary reconstruction for the MMC patient were likely initially aimed at protection of renal function and social continence with few considerations for eventual pregnancy. Although each reconstruction presents unique challenge, some concepts may be broadly applied for the MMC patient. Foremost is recognition that the greatest risk factor for worsening renal function in pregnant women with or without urinary reconstruction is preexisting renal insufficiency [32]. Significant pregnancy-related loss of maternal renal function along with development of new onset hypertension has been demonstrated, increasing the complication rates of preterm delivery and growth retardation [33, 34]. Superimposed on the issues of renal function is the recognition that many of this MMC population may have a solitary kidney due to congenital absence or loss from dysfunction [31]. It is critical to initiate assessment with a measurement of a non-creatinine-based estimate of glomerular filtration rate (GFR) as opposed to creatinine-based methods, as altered body habitus (atrophied lower extremities) and lower creatinine generation (nonambulatory) results in creatinine-based methods substantially overestimating GFR.

Combined with the increased risks for development of urolithiasis demonstrated for patients with urinary diversion are the complexities of the physiologic and anatomic changes which accompany pregnancy. Risk for both upper and lower urinary tract calculi in patients with bladder augmentation have been variably estimated from 9 % to as high as 50 % [35]. Although some hazard may be attributed to anatomic parameters such as incomplete emptying of continent reservoirs or native bladders, additional contributing factors include chronic bacteriuria, intravesical foreign bodies, mucus secretion, metabolic acidosis, enteric hyperoxalura, as well as the typical dietary culprits [36, 37]. Physiologic and anatomic changes which occur with pregnancy may exacerbate the complexities of the MMC predisposition for calculi. Notably, the extrinsic obstruction of the ureter by the gravid uterus against the pelvic brim may certainly exacerbate preexisting hydronephrosis and urinary stasis, potentially predisposing to worsening renal function or urinary infection in this vulnerable population. This hydronephrosis of pregnancy tends to worsen during weeks 20–28 of gestation requiring increased vigilance of monitoring during this period [38].

Fortunately, due to the protective effects of increased secretion of several inhibitors of urinary stone formation such as citrate, magnesium, and glycosoaminoglycans, even patients with a known history of stone disease do not experience an increased rate of urolithiasis during pregnancy [39]. However, management of the MMC patient with altered body habitus and potential urinary diversion status at baseline necessitates high levels of awareness and expertise with modes of diagnosis and management if development of clinically significant stones manifest during pregnancy. Of particular concern in this population is the altered sensory capacity to recognize upper tract obstruction which may delay care until sepsis and acute renal failure present, which may endanger the pregnancy.

There is little guidance with regard to the presence of a retained bladder for those patients with diversion without concomitant cystectomy. Some authors suggest that concerns involving a retained nonfunctional bladder, such as pyocystis, may unfortunately only become overt during pregnancy [31]. Optimal drainage of the native bladder with a patent urethra may be achieved during the acute phase with catheter drainage; however, this option will need to be individualized for each patient's clinical situation.

Notable matters in addition to hydronephrosis which may manifest during the MMC pregnancy include compromise of vascular perfusion of the diversion bowel segment, intestinal obstruction, stenosis or prolapse of a urostomy, compression of catheterizable channels, as well as metabolic complications [31]. Of particular interest in patients with ureterosigmoidostomy is the possibility of mechanical deformation of the sigmoid

or ureteral anastomoses, potentially resulting in disruption of the ureteral implants or incomplete emptying. Notably, rectal sphincter function necessary for appropriate function of the ureterosigmoidostomy may be compromised by vaginal delivery, leading to de novo urinary and potentially fecal incontinence [31].

Several reports exist regarding the effect of the expanding uterus on mesenteric blood supply to an intestinal segment previously utilized for bladder augmentation or urinary diversion. Reports have noted that the pedicle supplying an ileal conduit is displaced cephalad and lateral to the expanding uterus, whereas the pedicle usually remains anterior to the uterus following augmentation cystoplasty [40, 41]. Fortunately, it has been described in the majority of patients that pregnancy slowly increases tension on the mesentery, leaving ample time for adaptation [31]. Although it should always remain a consideration for delivery planning, it appears that adherence of the mesentery to the uterus is also rare [41, 42].

Patients without bladder neck closure may experience de novo incontinence secondary to pressure from the expanding uterus which in most instances is expected to resolve following delivery [43].

Intermittent Catheterization

Due to the expanding size of the gravid uterus coupled with frequently compromised body habitus and mobility, issues with intermittent catheterization may manifest as pregnancy progresses. These difficulties are not exclusive to compression of a continent catheterizable channel but may also present in patients utilizing their native urethra for catheterization.

Augmentation Cystoplasty and Pregnancy Testing

One specific caution regard the diagnosis of pregnancy in the MMC with an augmented bladder. Due to false-positive readings resulting from urinary changes following interaction with the bowel mucosa, urine-based pregnancy tests are not recommended and the use of serum human chorionic gonadotropin (HCG) is preferable [44]. Common practice for patients with bladder augmentations involves initial performance of urine HCG testing prior to any invasive, anesthetic, or radiologic procedures. If this preliminary test is positive, it is suggested this be followed with a serum HCG analysis, which is standard for obstetric practice to follow during pregnancy.

Continent Catheterizable Stoma

Patients with continent channels may experience de novo stomal difficulties during pregnancy [38, 42]. Such problems may be secondary to changes in body habitus, particularly if the channel is located in the right lower quadrant. Enlargement of the uterus may compress and stretch the channel, making catheterization increasingly difficult during progression of the pregnancy. Such channel changes are typically expected to resolve following delivery. Alternative catheterization techniques, such as use of a coude-tip catheter, may occasionally be necessary. If the patient remains with a patent urethra and the procedure is technically feasible, use of native urethral catheterization may be indicated. Occasionally, the increased intra-abdominal pressure of the uterus can result in stomal prolapse or parastomal herniation, which again the patient may anticipate to resolve following delivery.

Urinary Tract Infection

Perhaps the most prevalent concern for patients with MMC and urinary diversion during pregnancy is the management of urinary tract infection. In the general population, there is no difference in the incidence of asymptomatic bacteriuria between pregnant and nonpregnant women. However, most patients with a continent diversion or augmentation cystoplasty can expect chronic, or at the very least intermittent, bacteriuria related to clean intermittent catheterization. Although in many situations in patients with

bladder augmentation or performing CIC such asymptomatic bacteriuria is not treated, in pregnancy alternate considerations for fetal risk must be accommodated. It is well recognized that the rate of pyelonephritis during pregnancy increases to 16–18 % of women who previously underwent urinary diversion and such infections can lead to preterm labor, fetal wastage, and infants small for gestational age [31, 45]. A similar risk profile appears to be present following augmentation cystoplasty with several small series reporting up to 60 % rates of UTI and pyelonephritis [38, 41, 43]. Due to the potential catastrophic consequences of early pyelonephritis to the fetus, many physicians recommend use of daily antibiotics for these complex patients [32]. Of course, the potential teratogenic effects of the antibiotic compounds must be considered with such decisions [46]. One reasonable approach would be reserving daily antibiotic use to those patients in the highest risk categories, i.e., those with baseline or new onset hydronephrosis, multiple symptomatic infections, or a history of pyelonephritis before pregnancy. Other authors advocate culture surveillance and treatment only in the context of symptomatology, much as they would treat these patients outside pregnancy [32]. This debate remains active and no consensus of opinion exists; however, American College of Obstetricians and Gynecologists consensus panel for the treatment of asymptomatic bacteriuria in pregnant women with spinal cord injury recommends "Frequent urine cultures (with appropriate treatment) or antibiotic suppression." (ACOG Committee Opinion #275, September 2002, reaffirmed 2005).

Mode of Delivery

Equally controversial to the management of urinary tract infections is guidance regarding the mode of delivery for the infant. Before accurate counseling and planning for delivery, priority must be given to obtaining comprehensive records on prior surgical interventions and urinary tract evaluations including urodynamics and upper tract studies. Although often the complete operative record will not be available for review, obtaining as much primary source information regarding specific procedures cannot be underscored. Individual practice patterns for pediatric reconstruction in addition to often multiple operative revisions make understanding their anatomy a top priority for the adult urologist assuming their care.

Factors influencing the choice of delivery mode beyond the standard obstetric concerns include the type of diversion or prior surgical interventions, anatomical issues related to the underlying disease process of the MMC patient, as well as fetal presentation [31]. As mentioned previously, continence may be impacted during the post-vaginal delivery period for patients with native urethras or ureterosigmoidostomy and this information should influence patient counseling. Vaginal delivery is not contraindicated in patients with augmentation cystoplasty in the setting of a native bladder neck and urethral continence mechanism. However, for individuals with bladder neck reconstruction, vaginal delivery potentially carries a risk of injury to the pelvic support and continence mechanisms [31]. Although no consensus regarding risk expectations in this setting exist, data from a widely circulated survey regarding delivery mode for MMC with bladder neck reconstruction or artificial urinary sphincter indicated most practitioners would recommend cesarean section for these individuals [43]. Few reports of pregnancy in the setting of an AUS exist, but available data suggests that a functioning AUS does not impact the complication profile during pregnancy and delivery [47]. Caveats are readily noted in these studies, such as the avoidance of high forceps delivery, and clearly no consensus of recommendation exists as most of these observations are anecdotal due to the few women facing these dilemmas.

Previous incontinence procedures, most notably the prior placement of a pubovaginal sling, may also drive decisions regarding type of delivery. Some series have suggested that prior bladder neck sling does not preclude vaginal delivery due to risk of incontinence [48]. Literature reviews of the small patient numbers reported with pregnancy following synthetic mid-urethral sling suggest only moderate decrease in continence following either vaginal or cesarean delivery [49]. Overall, urinary continence rates of

91.7 % were noted during pregnancy and 80.6 % during the postpartum. The majority of women in these studies (58.3 %) proceeded with vaginal delivery. Certainly for patients with any prior incontinence procedure, risks of functional injury, and loss of continence with vaginal delivery should be discussed as they approach 19 % in the overall population [50]. Although impossible to generalize this data to the MMC population due to variation in risk factors, clearly some threat of continence disruption exists.

Discussion of long-term risk to continence and recommendation for the mode of delivery must be individualized. If vaginal delivery is primarily chosen, careful consideration must be given to avoidance of prolonged labor to reduce pelvic floor trauma. If cesarean section is chosen, emergent or elective, it is critical to involve a reconstructive surgeon familiar with the anatomy to reduce incidence of injury to the bladder or vascular pedicle. Patient proximity to appropriate levels of high-risk obstetric care may additionally drive decisions once labor has initiated as such patients may elect cesarean section in lieu of prolonged labor at a primary facility with the potential need for emergent cesarean section without appropriate adjunct expertise.

Patients with MMC frequently display elements of pelvic organ prolapse at baseline which may be exacerbated by pregnancy and both vaginal delivery and even cesarean section [31]. If the prolapse is significant enough to warrant operative repair prior to pregnancy, it may be prudent to avoid vaginal delivery as worsening of the prolapse may be inevitable in that setting.

Another prominent anatomic consideration includes bony and muscular anatomy and capacity to abduct the hips which may in some instance preclude capacity for vaginal delivery.

An additional challenge with vaginal delivery which may depend on the level of the spinal dysraphism is difficulty generating sufficient Valsalva effort required to progress through the later stages of labor [51]. Of course, the gravid uterus may exacerbate background restrictive airway disease by compressing the diaphragm and resulting in a potential for respiratory compromise.

As elegantly outlined by Hautmann and Volkmer [31], pragmatic concerns that dictate options for mode of delivery are outlined below:

Vaginal delivery should be considered contraindicated in the following MMC patients:

- Patients with a narrow bony pelvis
- Patients with artificial sphincters or bladder neck reconstructions
- Patients with contracted hips

Vaginal delivery should be performed with caution in the following patients:

- Patients with ureterosigmoidostomy
- Fetal malpresentation
- Patients with uterine prolapse

Likewise, the authors endorse following concerns should be noted for patients regarding proceeding with cesarean section:

- Patients with intraperitoneal VP shunts
- Patients with diversion pouches, enterocystoplasty, or neobladder

Technical considerations with cesarean section include performing the procedure via a high midline incision to avoid damage to the reservoir [42, 43]. Catheterization of channels in the immediate preoperative period may assist with either avoidance or recognition of injury induced by the dissection.

A particular item of concern when contemplating pregnancy and cesarean section in the MMC population is the presence of a ventriculoperitoneal (VP) shunt. VP shunts are common in the patient with MMC and hydrocephalus and malfunction during pregnancy may be associated with headache, nausea, and emesis, and even potentially impaired consciousness [52]. Functional obstruction due to the gravid uterus increasing intra-abdominal pressure or mechanical obstruction may additionally manifest in the aforementioned neurologic sequela [52–54]. Of significant concern is the potential for shunt infection during intra-abdominal surgery, particularly emergent cesarean section. This infection risk may be increased in the presence of prior urinary tract reconstruction with the possibility of spillage of contaminated urine into the peritoneal cavity containing the VP shunt.

Also dependent on the specific lesion level in MMC patients is the capability to detect the onset

of labor [55]. Curiously, although paraplegia does not appear to affect the contractility properties of the uterus, as mentioned above, the final stages of labor may be compromised due to deficits in the coordinated muscular effort necessary for the final stages of labor [55–57].

Conclusions

No issue with the transitional MMC patient rivals the complexity of considerations for the physician as those revolving around pregnancy. Outside of the incredible array of physiologic and anatomic parameters for consideration, the social and cognitive issues superimposed on this population creates additional layer to navigate. An overriding theme in the literature revolves around the lack of appropriate counseling of the MMC regarding sexuality, fertility, and pregnancy from their physician providers. It is imperative to view these challenges as opportunities to assist these patients in navigating the delicate topics of sexuality and pregnancy as embracing these topics may assist the MMC with transition to an adult individual care model from the family-centered pediatric model.

Summary

- Actively engage adolescent and adult patients in discussions regarding sexual activity, contraception, and fertility
- Engage multidisciplinary team for preconception counseling
- Maintain vigilance with regard to latex allergies and antibiotic prophylaxis
- Advocate high-dose folic acid use (4 mg/day)
- Monitor renal function, preferably with non-creatinine-based evaluation
- Caution with use of urine pregnancy tests with bladder augmentation patients
- Individualize risk management and mode of delivery to patient goals

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6 Revision Genitoplasty, Sexual Function, Fertility, and Pelvic Organ Prolapse in Exstrophy and the Management of Pregnancy

Dan Wilby and Dan Wood

Introduction

The initial goals of treatment of bladder exstrophy remain the preservation of renal function and obtaining urinary continence. If carried out in centres of excellence, surgery can achieve these relatively easy-to-measure goals in 70–80 % of children [1]. In adolescence and adulthood, once continence is secured, focus often shifts towards the cosmetic and functional outcome of the genitalia. The goals of additional procedures are to provide the external genitalia with an acceptable aesthetic appearance, to produce a functional vagina/penis for comfortable sexual intercourse, to retain sexually sensitive tissue for orgasm, and to preserve fertility potential. The results of genital surgery are difficult to assess in childhood, and pubertal growth can alter the final cosmetic and functional results of the initial reconstruction. Given that psychosexual development is only completed after puberty, problems may not become apparent until adolescence or early adult life. Now that patients are living independent long lives with bladder exstrophy following successful reconstruction, complex problems around pregnancy and delivery are evolving and becoming more commonplace.

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Genital Anatomy in Females

In exstrophy, the vagina, introitus, and anus are displaced anteriorly, the labia do not meet in the midline anteriorly, and the clitoris is bifid (Fig. 6.1). The labia are not fused anteriorly and there is an absence of a fourchette; 40–65 % of affected women encounter dyspareunia related to these anatomic differences [2]. The vagina is of normal calibre with reduced length; the introitus is very narrow because of the bulk of posterior tissue; the cervix is located in the anterior vaginal wall with a normal uterus above; the vaginal lies horizontally—i.e. parallel to the floor when standing [3]. The cervical prominence may be exaggerated by the absence of uterine supports—the cervix is often very low and close to the introitus. The pelvic floor is deficient—with most of the levator ani sitting behind the rectum and with a wide lateral deviation (Fig. 6.1).

As the child grows, the pubic diastasis widens—tending to widen the gap in the levators predisposing to the risk of prolapse and affecting the external appearance of the lower abdomen and genitalia. The midline scar is augmented by the widening and the mons pubis has limited hair

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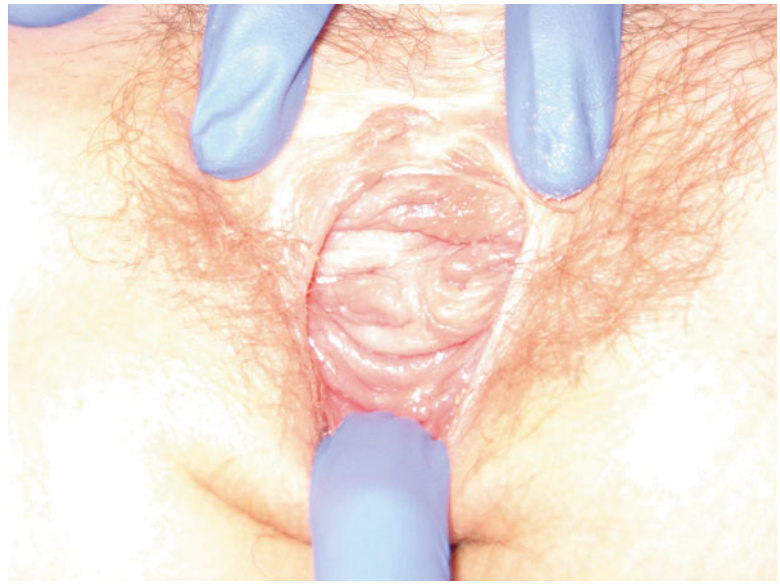

Fig. 6.1 The external genitalia of a female affected by bladder exstrophy. The bifid clitoris is seen along with a gap in the pubic hair

growth in the central portion. It is possible to rotate the hair-bearing skin into the midline with a view to improving this appearance. The external genitalia can become distorted with a resulting unacceptable cosmetic appearance.

Revision Genitoplasty in Females

At least 80 % of female patients treated for bladder exstrophy require revision genital surgery [4]. Given that such a high proportion of female patients require revision surgery, routine vaginal assessment at puberty should be undertaken in order to evaluate the potential for further reconstruction. The earlier any potential problems are addressed, the better the chance of normal psychosexual and social development. A common functional complaint is of introital stenosis, inadequate vaginal length or introital stenosis can result in dyspareunia or an inability to have penetrative intercourse. In one series, 32 % of young women underwent revision genitoplasty for this problem alone [5].

Reconstruction Techniques

Revision genital surgery can be utilised either to improve upon an unsatisfactory cosmetic appearance, but this is not essential. Correction of an introital stenosis is the most important reconstructive procedure that is undertaken in these patients.

Monsplasty

Through excision of the midline scar, the non-hair-bearing skin is removed and replaced with hair-bearing skin flaps based inferiorly or laterally that can be rotated together with their underlying fat to cover the defect.

Vulvoplasty

As in monsplasty, the midline scar is excised down to the bifid clitoris; the anterior aspect of the labia can be brought together to form a fourchette. The two clitorides can be joined by approximating the soft tissues without the need for sutures to be directly placed on the clitorides, thus minimising the risk of damage to the neurovascular supply [5]. It is worthy of note, there are no data relating to clitoral sensation following such reconstruction in exstrophy patients.

Vaginoplasty

Due to the presence of a normal calibre vagina above the introital stenosis in pure bladder exstrophy, the majority of patients are suitable for a relatively simple perineal vaginoplasty. Anecdote suggests that very few patients are able to have intercourse without some form of introitoplasty.

In exstrophy, a posterior episiotomy vaginoplasty or VY vaginoplasty is often all that is required to open the introitus. In the postoperative period, patients are taught to pass vaginal dilators to reduce the risk of re-stenosis. Other procedures, such as the laying in of a perineal flap, have been described—results are described as being good [5]. Whilst this may have the potential objective of reducing stenosis, this is not clear and sexual function is not detailed in their report.

Pelvic Organ Prolapse

The mean age to uterine prolapse in patients with exstrophy is 16 years [4] with a prevalence of 18 %; this can rise up to 50 % later in life. The prolapse is thought to occur due to the pelvic floor deficiency described above combined with a failure of the bony pelvis to form a complete ring anteriorly. Whilst the early osteotomy was not shown to decrease risk of prolapse, decreased pubic diastasis correlates to lower risk. It remains to be seen whether early mobilisation and reconstruction of the pelvic soft tissues (Kelly procedure) [6, 7] will reduce the incidence of prolapse. The traditionally described pessary treatment is often impossible due to a short vaginal length and the lack of pelvic floor musculature

Numerous techniques have been described for the treatment and prevention of prolapse, including fixing of the uterus to the abdominal wall in childhood [8]. This prophylactic measure proved to be a success and did not complicate pregnancy; however, this technique is not an effective treatment for existing prolapse. Robust long-term evidence regarding the correction of prolapse in the exstrophy population is sparse; a recent consensus suggests that suspension to the sacrum, when present, is likely to give the best results [9]. Various techniques have been described to achieve this, for example, the Gore-Tex® (W.L. Gore and Associates Ltd., Scotland, UK) wrap technique using a length of Gore-Tex® passed through the broad ligaments, around the cervix, and fixed to the sacral promontory. Data have shown a 75 % success rate over a mean follow-up of 8 years have been reported using this technique [10]. The technique of sacral suspension under its varied nomenclature (sacrocolpopexy, hysteropexy, sacrocervicopexy, etc.) is thought to have little or no deleterious effects on fertility; however, it should be deferred until a couple have completed their family. The risk is that during pregnancy or delivery the sacrocolpopexy would be disrupted leading to a recurrence of the prolapse and the need for a repeat procedure in a very complex surgical environment. When treating the prolapse, it is important not to remove the uterus as this not only renders the patient infertile, but is the only structure able to fill the pelvic floor defect. Without the uterus the potential for a large enterocoele exists, the treatment of which can be extremely challenging.

Revision Genitoplasty in Males

Historically, genital reconstruction in male patients was delayed until complete bladder closure or puberty but may now be undertaken with the initial surgery in the neonatal period [11]. Growing up with a normal appearing pendulous penis following reconstruction in the neonatal period has been said to have a positive effect on psychosexual and social development in these boys, the ‘true’ appearance and function of the penis is, however, not clear until puberty [12].

The classic appearance of the penis in a male with exstrophy is of a short (due to short corpora), broad, dorsally tethered penis, an open glans, absent dorsal prepuce, with a dorsal or ventral urethral meatus dependent upon the type and timing of reconstruction in infancy. Many erectile deformities have been described [13], but the majority are a consequence of surgery in infancy where the corpora may have been damaged, only dorsal chordee is an integral part of the exstrophy complex. Asymmetrical corpora are often encountered, where a scarred and fibrotic corpus can compound the deformity (Fig. 6.2).

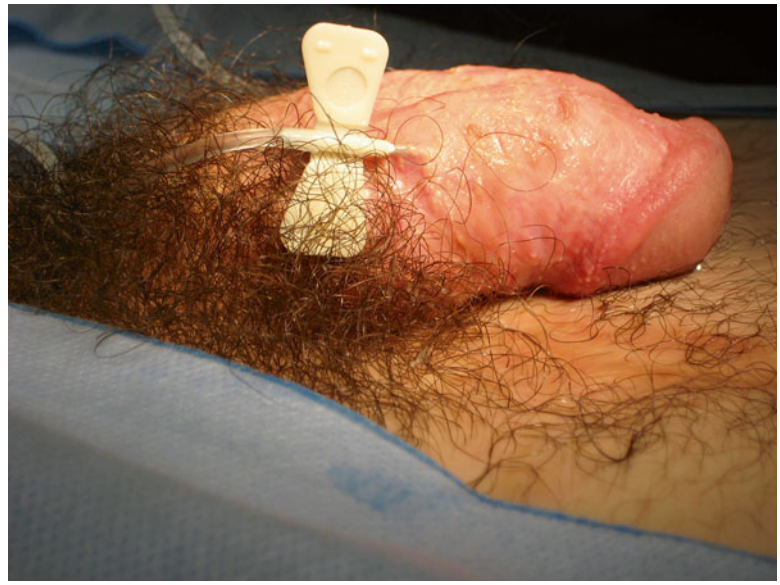

Fig. 6.2 An example of the dorsal chordee described. This may be as a result of skin tethering or urethral length restriction. A butterfly needle needs placing in both corpora to achieve an artificial erection as there is no cross-circulation

Assessment of Deformity

Before embarking upon reconstructive surgery, it is important to gain a good understanding of current function in terms of sensation, erectile function, ability to orgasm and ejaculate, and the presence of chordee or deformity that may or may not affect function. Establishing whether a deformity precludes penetrative intercourse or is purely a cosmetic problem is relevant, but both factors can be equally as important to patients. Dorsal chordee is a common finding in adolescent and adult men with exstrophy—this may be simple skin tethering, or depending on the reconstruction, the urethra may be the tether. In considering reconstruction, it may be necessary to relocate the urethral meatus. It then becomes important to consider future urethral function, i.e. if the bladder neck is closed and the urethra is to act solely as a seminal conduit, then if the meatus needs to be located in a proximal or hypospadic location it will have to stay there—further attempts to terminalise a 'dry' urethra will be unsuccessful with a high risk of stricture. If the patient is voiding urethrally or catheterising, further urethral reconstruction may be of benefit. The cosmetic appearance of the penis can be a major concern to the patient and should be considered carefully alongside function. An objective anatomical assessment can be made by performing an examination under anaesthetic with artificial erection.

Reconstruction Techniques

The aims of genital reconstruction in the male exstrophy patient are to provide a penis that is symmetrical and straight enough for penetration with normal sensation and good erectile function. Urethral function is important—in our series 70 % had undergone urinary diversion [14]; therefore, the urethra is dry and acting only as a conduit for seminal fluid. If the bladder neck has been reconstructed and the patient is continent but either voiding or catheterising urethrally, the management of the adolescent and adult patient will be different. Cosmesis is important—patients will often raise concerns about this. The details below will discuss what is achievable and those factors that may limit the reconstructive options. This should be achieved without compromising sensation or erectile function; this in itself can be challenging due to the positioning of the neurovascular bundles. The location of the bundles may vary considerably depending upon previous reconstruction; the unpredictability of their position renders them vulnerable during further surgery [15] (Fig. 6.3).

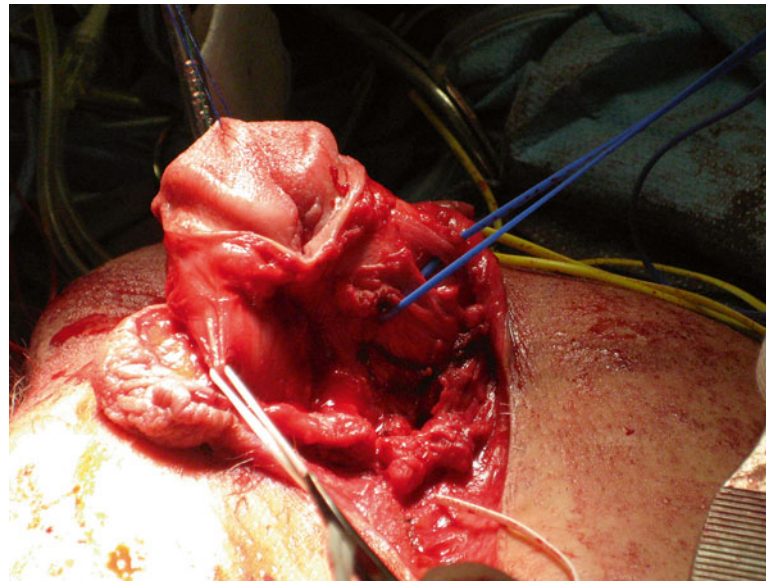

Fig. 6.3 Dissected exstrophy penis with the neurovascular bundles identified

Length

The corpora in men with exstrophy are 60 % shorter than normal corpora [16], and there are no buried corpora in the pelvis that can be utilised to increase true length. There is often asymmetry with one corpus scarred and fibrotic as a result of early surgery. Functional length may be improved by maximising exposure of the existing corpora; this can be achieved by releasing any corporal attachments to the body of the pubis and/or freeing of scar tissue that may be tethering the corpora. The former of these techniques does carry a risk of devascularising the corpora, especially if attempted in childhood [17]. An exstrophy penis can be reconstructed by complete disassembly—separating both corpora and as there is no cross-circulation between the two. In reconstruction, corporal tucks will straighten curvature and rotation either in or out of the corpora may improve length. In addition to these techniques, radial artery-free flap phalloplasty can be performed; this was first reported by de Fontaine et al. in 2001 with reasonable functional and cosmetic results [18]. Although it may be technically possible to perform a phalloplasty, this should be reserved for a patient whose penile anatomy or function prevents penetrative intercourse despite exploring the above penis-conserving techniques.

Chordee

The simplest form of correction of dorsal chordee is release of any scar tissue causing tethering using a VY or Z plasty technique. Correction of the corpora can either be achieved by shortening the convexity or lengthening, the concavity, or a combination of the two.

In shortening the convexity, some shortening of penile length is to be expected; the advantage of this method is that the urethra need not be disturbed. This is usually achieved by placing plication sutures in the corpora and has the advantage of requiring minimal dissection and little risk of damage to the neurovascular bundles; the clear disadvantage is the loss of length in an already short penis. In undertaking this type of surgery, the potential for complete disassembly needs to be available, and there may be a need to relocate the urethral meatus further proximally on the penile shaft. If this is a dry, seminal conduit, it should remain here. If it is used for urethral voiding, a further two-stage reconstruction may be possible. The issue of shortening and loss of sensation needs to be discussed during consent, but if there is a fixed dorsal chordee this needs correction in order to achieve any functional length.

In lengthening of the concavity, the corpora are incised transversely and closed longitudinally, ideally to each other after rotating the

corpora towards each other (the Cantwell–Ransley technique [19]). When using this technique, good apposition needs to be achieved; if the corpora are spread too far apart and apposition is not optimal, a new hourglass deformity can result. If the urethra is functional, complete, and dorsal, lengthening the concavity can result in apparent urethral shortening that requires urethroplasty to correct. In addition to Ransley's modification of Cantwell's technique first described in 1895 [20], various other methods for epispadias repair and correction of chordee have been published. Techniques such as those described by Mitchell [21] and Kelly [22] both involve complete penile disassembly with subsequent anatomical reconstruction. In Mitchell's procedure, the penis is divided into two separate hemicorporeal glanular bodies and a separate urethral plate. The advantage of this technique is that it does not require mobilisation of the neurovascular bundles or corporotomy, but does allow anatomical reconstruction of the penis with correction of rotational deformity and of chordee. The associated morbidity and necessity of these more invasive and complex procedures should be carefully considered when selecting the best reconstructive options [16].

Sexual Function and Fertility

The beginning of relationships and sexual function become important to all during adolescence. It is normal for any adolescent to question their function in relation to this and for many there will be moments or periods of insecurity. This is part of normal development. It is also normal to ask how a congenital anomaly and the treatment of it, including surgery, will affect sexual function. There is often a significant focus on cosmesis and in the case of a male patient penile size. In exstrophy, the bony diastasis may lead to a significant dip in the skin and a midline separation of the pubic hair. The long-term management issues with respect to sexual function have not been extensively studied but disorders or anxiety surrounding sexual function in adolescence can have a significant psychological impact on patients. Reports suggest that some 1/4–1/2 of patients are dissatisfied with penile length or chordee [16]. Libido in exstrophy patients is normal and they form normal relationships; in the author's experience a key component in sexual function is the partner's understanding and acceptance of the patient's reconstructive history. In a society where casual sexual encounters are more common, this can create a pressure on these patients. A desire on their part to conform to the behaviour of their peer group is met with a fear that a new partner may not understand their condition and rejection may result. The treating urologist needs to be aware of this background and prepared to manage it. A multidisciplinary approach, including psychosexual counselling and support, should be adopted as discussing and addressing issues around sexual function can be challenging for both the patient and clinicians.

Table 6.1 Semen analysis and fertility in male patients with exstrophy results of nine series [23]

Semen	Reconstructed	Urinary diversion	Undefined
Azoospermia	12	17	3
Poor			1
Good	3	11	
Paternity	5	12	2

Male Factor Fertility

It is likely that males born with bladder exstrophy have normally functioning gonads at birth, but there are no data to confirm this; in a review of nine reported series approximately half of patients were found to have azoospermia on subsequent semen analysis [23]. Patients who underwent early urinary diversion rather than reconstruction had more favourable semen parameters and paternity rates (Table 6.1). One hypothesis to explain this might be the deleterious effect of repeated prostatic and bladder infections. A significant limitation to fertility undoubtedly lies with the delivery of sperm, this can be considered in three stages; erection, adequate vaginal penetration, and ejaculation.

The anatomical mechanisms for erection are usually preserved in these men and organic causes

of erectile dysfunction are considered rare. However, when compared using the international index of erectile function–15 (IIEF-15), 58 % of exstrophy patients have erectile dysfunction compared to 23 % of controls [24]. Psychological causes for erectile dysfunction are much more common and are often linked to concerns about body image. When considering treatment for erectile dysfunction in an exstrophy patient, the same approach should be used as when treating other men. One important consideration is the lack of cross-circulation between the corpora; if intracorporeal prostaglandins are being used, then each corpus needs to be injected separately.

Patients with exstrophy can experience normal orgasm, but the proportion of males who have normal ejaculation is low. There are a number of reasons why this might be true. The absence of the bulbocavernosus muscles coupled with urethral scarring from reconstruction result in a lack of propulsion. The reconstructive surgery at the bladder neck may also have an effect. This tends to result in a viscous ejaculate that may not be expelled. There is conflict within the published literature with regard to the exact aetiology of the impaired ejaculation and its association with previous reconstruction versus urinary diversion. It is postulated that patients who have a diversion rather than reconstruction tend to maintain better ejaculatory function and have a higher fertility rate; there is also some evidence to the contrary that suggests cystectomy may be the cause of infertility; at the time of writing, there remains no consensus [25, 26]. Complete absence of ejaculation is rare, but it is often slow and without force; some patients describe a persistent small leakage of semen from the urethra. Annecdotally, patients may complain of pain at the time of ejaculation. This may be with or without a visible ejaculate. For those who have little or no seminal fluid expelled, obstruction at the bladder neck may be causing an accumulation within the seminal vesicals. This may result in spontaneous fistulation in the suprapubic region. Occasionally, it can be drained by the creation of an iatrogenic seminal fistula or conduit. This is not something that appears in the literature, but we have encountered it in our patient group.

Female Factor Fertility

As in males, fertility in females is limited predominantly by anatomical factors, unless there are co-existing urogenital anomalies that may result in infertility of gonadal origin, or obstructed menses, for example. Historically, female patients with exstrophy have been considered to have normal fertility provided intercourse is possible and semen can be delivered near the cervix. Historically, the location of the cervix in a relatively superficial position on the anterior wall of the vagina in these patients was thought to enable them to become pregnant with relative ease, and that this should be explained to patients at an early stage in their sexual development. Deans et al. found evidence to the contrary, in their series they identified a higher rate of delayed fertility [27] than in previously published reports [28–30] that was attributed to previous surgery and concomitant disease. Of the patients who had tried to conceive, 19/38 (66 %) were successful, only 4/19 within 1 year, and 2/19 patients had successful fertility treatment.

Assisted Fertility

The investigation and management of fertility disorders in patients with exstrophy is the same as in the general population. A careful history should be obtained to establish whether adequate penetration and ejaculation is being achieved. Simple measures such as the timing of intercourse around the fertile portion of the menstrual cycle and the female lying with the pelvis elevated after intercourse should be trialled. In patients who are able to produce an ejaculate that contains viable sperm but conception has failed due to inadequate delivery of sperm to the partner's cervix, a form of artificial insemination can be used. Ejaculated semen can be collected in a syringe and deposited in the vaginal vault at the appropriate time in the partner's menstrual cycle. Many patients will try this without reverting to further investigation, however if that is not the case baseline fertility can be assessed by offering a semen analysis.

If these measures fail, both partners should be investigated, preferably within a specialist fertility service.

The Management of Pregnancy in Exstrophy

Patients with complex urological anomalies including classical bladder exstrophy are now living normal independent lives with reconstructed urinary tracts. There is evidence that this patient group is fertile and has healthy babies [31]; however, the pregnancy and subsequent delivery can produce its own unique potential problems.

Robust data regarding the impact of pregnancy on the upper and lower urinary tracts and delivery methods is scarce in this patient group.

Factors to consider include: the timing of the pregnancy, the impact of pregnancy on the urinary tract, who should manage the pregnancy and where should this be done, what monitoring methods and schedule should be employed throughout the pregnancy, and what is the safest method of delivery.

Prior to Pregnancy

In the adolescent patient, the topic of pregnancy and its implications and potential complications has rarely been introduced during their paediatric urological experience. Educating patients about the potential impact of pregnancy and delivery on their urinary tracts is vital; it is clearly more preferable for this to occur before pregnancy but not always possible.

The use of the urine HCG test is notoriously unreliable in a population with reconstructed bladders due to 57 % false-positive rates. This is thought to be as a result of a reaction between the reservoir mucous and the reagent [32, 33]. Patients need to be informed of this and advised to have a serum HCG test if pregnancy is suspected; this can avoid unnecessary anxiety and misdiagnosis.

The timing of pregnancy, if it is a planned event, in relation to possible further urological reconstructive surgery that may be needed or likely to be required in the future is an important consideration. The patient needs to be aware of the potential impact of the pregnancy and delivery on their urinary tract. It would appear sensible, for example, if non-urgent surgery was being planned, to defer this until the patient had completed her family. The biggest consideration relates to the function of the drainage conduit, especially a Mitrofanoff and pelvic organ prolapse—as discussed above.

During Pregnancy

There is evidence to suggest that there is an increased incidence of UTI, pre-eclampsia, and upper tract obstruction during pregnancy in this group [31]. This group of patients require close monitoring during pregnancy to detect these problems early and intervene as required. An example of this would be a review at 20 weeks of gestation with an upper tract ultrasound, blood pressure monitoring, urine culture, and subsequent reviews at 4-weekly intervals with repeat investigations. This allows the multidisciplinary team to maintain close eye on renal function—indications to consider intervention would include a creatinine that does not fall as expected (with the physiological dilution of pregnancy), loin pain and persistent or worsening hydronephrosis on ultrasound (ensuring the bladder is empty).

The character of the bladder and outlet may change. Those that are normally dry may suffer renewed incontinence—as may be seen in unaffected pregnant women. The need to empty the bladder or reservoir may increase in frequency. Provided these are not coupled with other symptoms of infection, then there is only need for reassurance. For some women, the amount of mucous production may increase during pregnancy. Again, whilst this may be a nuisance intervention should be kept to a minimum—increased fluid intake is the most important factor, and additional bladder irrigation may be necessary for a few.

The function of a Mitrofanoff channel may change as a result of the mass-effect created by the gravid uterus. The channel may become progressively more difficult to catheterise as a result of kinking or being pushed to one side. The frequency

of catheterisation may need to increase as described above, and the length of the channel may increase requiring the longer length (50 cm) catheter. Our experience has been that it is very difficult to predict who will encounter these problems. The value of close surveillance by the team especially the specialist nurses is invaluable to the care of these women through pregnancy.

Delivery

As a whole, this population benefit from a planned caesarean section by an experienced team including a urologist specialising in reconstruction [34]. Morbidity can be reduced by minimising the risk of inadvertent damage to the reservoir and/or Mitrofanoff channel by employing this approach. The most important criterion is to avoid an emergency caesarean section without appropriate support. Our data suggested that this lead to an increased risk to both mother and baby [27]. For this reason, we aim to plan an elective caesarean section at approximately 37 weeks. Thus, the standard of care adopted by our unit is that of shared care (urologist and obstetrician) with close monitoring and support throughout pregnancy and delivery. It is a commonly asked question about the high rate of bacteriuria in reconstructed bladder and whether patients should automatically be given prophylactic antibiotics throughout pregnancy. It is recognised that the rate of urinary tract infection is high (up to 52 % compared to 2 % in the general population) [31]. Our practice has not been to do that for fear of selecting resistant bacterial strains. If a patient develops a urinary tract infection, then they should be treated and the case for prophylaxis discussed with microbiology and the obstetric team.

Number of Pregnancies

There is no prescribed or evidence-based limit to the number of pregnancies possible for women with bladder exstrophy or any other form of urological reconstruction. There are factors that both the patient and the caring team should consider. One would be the tolerability of uterine prolapse if present [35]—it is seen in 52 % in our series and may precede the first pregnancy [27] It can be extremely uncomfortable but definitive surgical intervention should be avoided until a family is complete for the reasons discussed above. A second factor will be the impact on the kidneys of previous pregnancies. History of a requirement for percutaneous nephrostomy tubes during a prior pregnancy risks a need for these in future pregnancies. Data are very limited for this specifically but there is a need to carefully monitor these women once they are pregnant. It is not safe to assume that because a first pregnancy was straightforward that a second will also be so. Finally, the surgical difficulty at delivery may influence the sense or not of a further pregnancy—very dense adhesions or complications requiring surgical revision (such as fistula) may make it sensible to advise against further pregnancy. None are absolute but all are important and when planning or discussing pregnancy should be discussed with a patient.

Summary

- Both male and female exstrophy patients may be capable of normal fertility—some may suffer impairment or delay and will need the support of a fertility team in achieving conception
- Penile reconstruction may be necessary as a result of dorsal curvature (the most common problem)—surgeons need to be careful to identify the neurovascular bundles. Evaluation with artificial erection may be necessary.
- In females, the vaginal introitus may be narrowed and need opening with an introitoplasty. Uterine prolapse is a common problem but should not be corrected until after a woman has completed her family.
- Pregnancy should be under the shared care of a urologist and obstetrician. Diagnosis should be with a serum hCG if bowel has been used to reconstruct the urinary tract. Delivery should be offered as an elective caesarean section

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7 Issues in the Long-Term Management of Adolescents and Adults with DSD: Management of Gonads, Genital Reconstruction, and Late Presentation of the Undiagnosed DSD

Martin Koyle and Paul Bowlin

Background

Disorders of sexual development (DSD) present a medical challenge on multiple levels. Prompt recognition of a disorder and appropriate diagnosis leading to individualized medical/surgical management are complex tasks. In older patients especially, these factors may potentiate the already significant psychological stress that has impacted the parents and family. Diagnostic and management controversies have existed since these conditions were first described. Today, as much as ever, the concept of what defines an individual's sex is heavily debated, and hence have issues related to the timing and appropriateness of any interventions. In fact, in some conditions, therapeutic delay is now considered an alternative so that surgery, once commonplace in infancy and childhood, is now offered after puberty (e.g., gonadectomy in complete androgen insensitivity syndrome). As we gain more knowledge and our long-term experience with these conditions broadens, we recognize that there are many issues that persist or develop in the adolescent and adult period that require careful discussion and potential surgical intervention. Indeed, previously unrecognized cases of DSD may present after childhood, raising unique considerations. Thus, the surgeon who once dealt primarily with DSD in infancy must be cognizant of the ever-changing guidelines and opinions related to the various disorders and engage the adolescent and young adult in the options available and the informed consent process. From a surgical standpoint, one needs to be able to manage issues pertaining to the gonads and genitals (internal and external) in established as well later presentations of previously undiagnosed DSD.

Fertility

There are many issues to consider, with regard to the gonads, when caring for adolescent/adult with DSD. In this era of multidisciplinary DSD teams, the discussion about the evaluation and management of the gonads is typically had early in the patient's life with the team and the patient's parents/guardians with subsequent management guided by those discussions. When caring for an adolescent/adult, the provider is often left addressing the outcome, good or bad, of decisions that were made early in the patient's life. Hence, one must provide information regarding issues of fertility, gonadal function, gender correspondence, and risk of malignancy when considering gonadal management.

In the age of advanced reproductive techniques, the fertility potential for some individuals with

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DSD has been greatly increased. Although not considered as a DSD, individuals with Turner syndrome, for example, have been able to achieve pregnancy [1]. The cost and complexity of achieving a pregnancy however may practically preclude reproduction for many of these individuals [2]. In many DSD conditions, such as congenital adrenal hyperplasia (CAH), rates of spontaneous fertility correlate to the severity of the underlying condition [3, 4]. Early studies revealed an overall fertility rate of <10 %, but this data is hampered by the fact that many individuals with CAH do not attempt to reproduce [5]. More recent studies reveal much higher pregnancy rates in those with salt-wasting CAH than simple virilizing CAH [5, 6]. In a recent study of 81 salt-wasting CAH patients only nine had attempted to become pregnant with eight of them successfully conceiving [6]. The data for males with CAH is less abundant but suggests a trend toward impaired fertility. One recent study noted out of 203 patients, only 37 % had attempted to conceive. Of those attempting however, 67 % had been able to successfully impregnate their partner [7].

Other DSD patients being raised as males also present fertility challenges related to impaired testicular function as well as the effects of testosterone replacement. In gonadal dysgenesis, syndromes with one-streak gonad and one dysgenetic gonad (mixed gonadal dysgenesis) or two-streak gonads (46XY gonadal dysgenesis) germ cell and androgen synthesis after puberty is often inadequate. Resultantly, testosterone is frequently needed to help complete puberty and is continued throughout adulthood in order to treat persistent hypogonadism [8]. As a result, fertility status is impaired. Much data are lacking as, in the past, many of these children who might have been reared as males were reassigned gender. There have been reported cases of successful extraction of sperm [9] in the mixed gonadal dysgenesis (MGD) adult population, but progression to pregnancy is rare [10]. A recent study of 20 MGD patients did not demonstrate any of them to be successfully fertile [8]. Whether such advances in assisted reproductive technology (ART) will be translatable to MGD patients has yet to be explored in large numbers.

Individuals with Klinefelter syndrome have associated azoospermia and are traditionally considered infertile. Advances in reproductive technology, specifically testicular sperm extraction (TESE) and intracytoplasmic sperm injection (ICSI) have demonstrated an ability to retrieve sperm, which have then been shown to lead to successful pregnancies and births in this population [11]. In the 5α-reductase type II deficiency (5αRD2) population, fertility is possible given that these individuals are chromosomally normal males. The commonly associated, and often late corrected, cryptorchidism however frequently has an impact on spermatogenesis with resultant impaired fertility [12]. Complete androgen insensitivity syndrome (CAIS) is currently considered a condition for which infertility is certain given that these individuals are generally raised as females but do not possess any internal female reproductive organs and have dysgenetic male gonads [13]. Whether these dysgenetic gonads could be used to obtain spermatogonia has not been demonstrated to date. There have been reports however of successful reproduction in pure gonadal dysgenesis patients using donor oocytes with stimulation of the patient's hypoplastic mullerian structures [14]. Fertility in cases of partial androgen insensitivity syndrome (PAIS) has been successful but requires the use of ART [15].

Hormonal Function

The hormonal function of the gonad(s) is an important consideration that has implications related to the individual's assigned sex, physical and social development, and future fertility. The type and timing of hormonal replacement should be consistent with the assigned sex and expectation for onset of puberty [16, 17]. For DSD patients being raised as males, testosterone therapy is typically initiated in an effort to induce puberty and promote appropriate pubertal development. This is not always necessary, as some 46XY DSD patients will have enough testosterone production to stimulate puberty. A 2011 study noted only 26 % of these patients were able to

induce and complete puberty without testosterone supplementation [18]. While intramuscular injections are commonly used, oral and transdermal replacement has also been reported [19]. In conditions such as 5αRD2, replacement of the active androgen, dihydrotestosterone (DHT), has also been reported [20]. In those being raised as females, hormone replacement with estrogens and progesterones is being used to induce puberty and menses in those with a uterus [16]. The delivery route and type varies but is generally via an oral or transdermal route [21]. Dosing adjustments and monitoring are important once hormone replacement has been initiated. Conditions such as partial androgen insensitivity syndrome (PAIS) may require excess testosterone replacement in order to achieve a clinical response [22].

Durability of testosterone production with aging for the rare DSD diagnoses with adequate testosterone production at the time of adolescence has not been studied. Given this, it is prudent to consider testosterone screening and replacement if needed as these patients enter middle- and late-adulthood.

Malignancy

The risk of malignancy arising from the gonad(s) of an individual with DSD is heavily dependent on the specific condition and attendant genotype. Broadly speaking, any individual with a dysgenetic gonad has at least a theoretical risk of malignancy if their genome contains any Y chromosome. As such, it is paramount to clearly define an individual's karyotype in order to detect the presence of Y chromosome material. The risk of malignancy is variable depending on the condition. The highest risk groups are [16]:

- Gonadal dysgenesis who have intra-abdominal gonads and are gonadoblastoma locus on the Y chromosome (GBY) positive
- PAIS and non-scrotal gonads
- Individuals with Frasier or Denys–Drash syndromes

In general, the more ambiguous the genitalia in the presence of a Y chromosome and non-descended gonad, the higher the risk of malignancy [23]. In these cases, gonadectomy is recommended as early as possible. Moderate-risk individuals include those with streak gonads in the presence of a Y chromosome (e.g., MGD, Turner syndrome mosaics). These streak gonads are generally recommended to be removed during childhood but with less urgency than the higher risk groups. For low-risk groups, particularly CAIS, the timing of gonadectomy is debated. Classic management recommended removing the gonads as soon as the diagnosis of CAIS was confirmed. More contemporary review however advocates delaying gonadectomy until after puberty given that the aromatization of testosterone to estrogen can be advantageous in helping to initiate puberty [16]. This perceived low risk of malignancy, in one reported series of CAIS patients, has led to many individuals choosing to keep their gonads indefinitely. This same report however suggests that the relatively low risk of malignancy in CAIS may be a significant underestimate, with their included review of the systematically selected literature [24–27] revealing 14 tumors in 98 adult patients (14 %). Accordingly, the authors caution against any dramatic shifts in management given the relative difficulties in diagnosing malignancies in these residual gonads [28]. Indeed, while the risk of malignancy is low, it is in no way inconsequential. This is especially true given how difficult it is to monitor a non-palpable gonad for signs of malignancy. The 2006 Consensus statement on management of intersex disorders summarizes the risk of malignancy in various DSD conditions as shown in Table 7.1.

As individuals with DSD mature, it is important to make them aware of the risk of malignancy in their remaining gonads, if present. Providers need to stress the importance of routine self-examination and prompt evaluation of any abnormalities. In situations where the diagnosis has been delayed, in a patient with a significant risk of malignancy, gonadectomy remains a key priority.

In the event that gonadectomy is required, it is important to consider the surgical approach, which is dependent on the age and size of the patient as well as the location of the gonad(s)

Table 7.1 Gonad malignancy risk in DSD

Risk group	Disorder	Malignancy risk, %	Timing of gonadectomy
High	GD (+Y) intra-abdominal	15–35	As early as possible following diagnosis
	PAIS non-scrotal	50	
	Frasier	60	
	Denys–Drash (+Y)	40	
Intermediate	Turner (+Y)	12	Childhood
	17β-hydroxysteroid	28	
	GD (+Y) scrotal	Unknown	
	PAIS scrotal gonad	Unknown	
Low	CAIS	2	Debated
	Ovotesticular DSD	3	
	Turner (−Y)	1	
None	5αRD2	0	Unnecessary
	Leydig cell hypoplasia	0	

Adapted from 2006 International Intersex Consensus Conference [16]

being removed. Traditionally, exploration was carried out via an open incision but inguinal and translabial/scrotal approaches have also been described [29]. Currently for adolescents and adults, the most widely used approach is laparoscopy. A laparoscopic approach has the advantage of being able to diagnose and treat gonadal issues while leaving only subtle scars [30].

Genital Reconstruction

In many DSD conditions, genital reconstruction is accomplished early in life. In these individuals, there can be numerous issues related to the initial reconstruction during the progression from childhood to adolescence and adulthood. For vaginal reconstruction, these late issues can include: unsatisfactory cosmesis, vaginal stenosis, clitoral atrophy, clitoromegaly, lack of sensation, dyspareunia, and excess mucus production [31]. In penile reconstruction, late issues can include: unsatisfactory cosmesis, urethral fistula, urethral stenosis, penile torque or curvature, and lack of erection and/or sensation.

Female Phenotype

There are numerous studies of the long-term outcomes of childhood feminizing surgery demonstrating high rates of success [32, 33]. Other studies however suggest that the need for revision reconstruction is as high as 98 % [34]. Burgu et al. reviewed a 15-year experience with vaginoplasty in 63 patients of whom over 50 % had an underlying DSD diagnosis. They noted an overall complication rate of 73 % with 11 % of patients requiring a secondary procedure. The most common complications were vaginal stenosis, discharge, and prolapse of the mucosa. Skin flap vaginoplasty was the technique associated with the highest revision rate (16 %). Of those seven patients requiring revision, two had revision of the flap and five were converted to an intestinal segment neovagina. They noted a significantly higher complication rate in those undergoing surgery before puberty vs. postpuberty (57 % vs. 15 %) [35]. Hoepffner reported on 58 patients with DSD and reported a similar rate of need for revision vaginoplasty (12 %) [36]. Many advocate performing the reconstruction as a staged procedure with clitoroplasty early in life followed by vaginoplasty in adolescence or beyond given that the vagina has no functional purpose in childhood. Those in favor of early reconstruction cite the advantages of improved tissue mobility and healing along with the option to utilize the preputial tissue from the clitoroplasty to reconstruct the distal vagina [29]. Advocates of delayed reconstruction champion the ability of the patient to be involved in the discussion about gender, surgical options, and the ability to comply with postoperative care such as vaginal dilation.

In patients that have undergone early clitoroplasty, there is evidence that the clitoral sensitivity is diminished, in comparison to similar patients who have not undergone clitoroplasty [37]. Unfortunately, this issue cannot be directly addressed through revision surgery as the underlying problem, damage to the neurovascular bundles, cannot be reversed.

Another issue, patient dissatisfaction with genital cosmesis, is often raised and potentially addressed with revision surgery. In one large series, 41 % of patients reported that their perception of the overall cosmetic outcome of their reconstruction was poor [34]. Much of the cosmetic dissatisfaction centers around the size of the glans clitoris but can also focused on the labial tissue. Concerns about the labia generally relate to the relative paucity of redundancy of labial tissue. As with many cosmetic issues however, it is important to recognize that there is wide anatomic variation in female genetalia in general [38].

Surgical techniques to address vaginal reconstruction, or revise surgeries performed early in life, include the use of perineal dilation, bowel, skin, and oral mucosa [39–42]. Passive dilation of the perineum, resulting in a progressively deepened neovagina, has been accomplished with a variety of techniques such as repeated pressure with serial vaginal dilators [39], regular coitus [43], repeated pressure with a dilator attached to a bicycle seat [44], and surgically placed traction devices [45]. Peña has described techniques to mobilize the urogenital sinus as a unit, either in total or partially, to help avoid separating the vagina from the urethra [46]. This mobilization can be combined with flap-based repairs to help bridge additional distance to the perineum. A variety of bowel and skin substitution techniques have also been described. One of the earliest references from 1904 describes the use of ileum [47]. Later techniques involved similar interposition using segments of the sigmoid colon or rectum [48]. Skin, either as a split or full thickness graft, or flap has been described, typically in combination with a vaginal stent to aid in dilation [41]. Reconfiguring and dilation of peritoneum has also been successfully utilized [49]. The use of oral mucosa for revision vaginoplasty has been shown to be a successful technique, at least in the short term [42, 50]. In complex primary repairs, such as with a high urogenital sinus, or revision operations, utilizing approaches such as the posterior sagittal approach [51] and anterior sagittal transrectal approach (ASTRA) can be advantageous [52]. Early results from the ASTRA technique demonstrate a high rate of success without fistula, continence issues (urinary or fecal), or strictures [53]. As with any early repair, only prolonged follow-up will demonstrate the overall success, particularly with regard to stenosis. A multitude of other techniques and variations of older techniques have been employed with no clear consensus on the most successful approach.

The most challenging long-term complication of any vaginoplasty repair is stenosis. In less severe cases, this is often managed with vaginal dilation. More significant stenosis however, often requires surgical re-intervention. Often times, the scarring process of the stenosis limits the surgeon's abilities to utilize local tissues in the revision repair. In these situations, the use of a substitution technique [48] or oral mucosa [42] has been successful. Long-term complication rates are difficult to quantify given the heterogeneity of the available data and tendency to report on case series and single surgeon experience. A recent systematic review evaluated 162 publications in an effort to understand the immediate and long-term success of reconstructive techniques for vaginal agenesis. Scarring was one of the most frequent complications in the graft-based repair techniques. Discharge and prolapse were more common in the substitution technique studies [54].

The presence of urinary system issues is another potential problem that results from the underlying DSD as well as reconstructive procedures. Studies in females with CAH and androgen insensitivity syndrome have shown varying results however with some citing and increased frequency of lower urinary tract symptoms (LUTS) [55] but others showing relatively equal frequencies of LUTS between those having undergone feminizing genitoplasty and controls [56].

Male Phenotype

Complications with male reconstruction occur in a bimodal distribution. Lack of long-term studies impairs our ability to understand late natural history of repairs, so our best understanding rests in studies with shorter term follow-up. These include: urethral fistula, urethral stricture, sacculation of reconstructions causing urinary stasis and recurrent infection, development of hair balls and stones in the reconstructed urethra, chordee, scarring, ejaculatory complaints, among other issues. A full discussion of long-term outcomes of hypospadias repair can be found elsewhere in this textbook in chapter 8 (Hanna and Cambareri). When reconstruction is performed later in life, the success rate can be negatively impacted, particularly with regard to wound healing, infection, complications, and overall success rates [57]. There are hundreds of described techniques for addressing the primary repair as well as revision repairs [58]. Much of the early salvage experience involved the use of local skin flaps, which has been associated with long-term failure need for additional revision [59, 60]. The use of grafts, particularly oral mucosa has proven to be a much more successful technique for addressing the salvage urethroplasty [61, 62]. The use of oral mucosa has been described for both single and multiple stage procedures with some data to suggest higher success rates for the most complex revisions using a staged technique [59]. Urinary symptoms, sexual function, and self-esteem issues are all possible and frequently require additional intervention [63]. While urinary tract outcomes for DSD patients raised as males is limited, data from the hypospadias population has demonstrated a significantly higher frequency of urinary issues such as spraying, post-void dribbling, and a sensation of incomplete emptying [64]. As the quality of long-term data improves, it is also becoming clear that adults who undergo hypospadias repair during childhood frequently have functional and emotional issues that carry into adulthood [65, 66].

For individuals with severely undervirilized male 46XY DSD conditions, advances in phalloplasty have allowed for the creation of a functional penis. The majority of this data comes from Gent University Hospital in Belgium. A recent update from this group champions the radial forearm flap as the current gold standard for phalloplasty. In their series of 316 patients, after the required two operations (phalloplasty followed by penile implant), all were able to void in a standing position and most were able to experience sexual satisfaction [67]. As a recent summary of key discussions from a prominent DSD conference highlights, the incorporation of native genital sensitivity tissues is an important consideration when deciding on phalloplasty options [68].

Long-Term Quality of Life

Masculanizing and feminizing surgery remains a topic of great debate given the potential for delayed or long-term sequelae as it pertains to sexual function, sensation, and quality of life (QOL). For clitoral surgery performed in childhood, there is data showing a reduction in the ability to achieve orgasm along with impaired sensitivity and sexual satisfaction [37, 69]. While there have been studies and techniques described to help preserve sexual function [70], there is little long-term data that definitively demonstrates preservation of sexual function following genitoplasty [37]. Data on overall QOL is more variable with most of the outcomes measured in the CAH population. Some of these studies show little to no compromise in QOL metrics [71, 72], while other studies find significant detriment to QOL as a result of surgical intervention [7]. The results of these, and other QOL studies pertaining to CAH patients, are nicely summarized in a paper by Zainuddin et al. [73].

The impact of medical and surgical management of individuals with DSD raised as males has also been shown to have long-term QOL and sexual implications. Most studies reveal a negative impact on sexual function, satisfaction, and quality of life as it pertains to hypospadias repair [74]. Similarly, studies have demonstrated lower frequency of ejaculation and orgasm in hypospadias patients [75] and a higher incidence of

erectile dysfunction [76]. In one small study of patients with partial androgen insensitivity, there was notable impairment in sexual satisfaction and erectile function [77]. Overall however, the availability of long-term QOL data, as it pertains to male reconstruction specifically in DSD populations, is quite limited and thus there is little current ability to make revised treatment recommendations [78]. As recent review notes, this paucity of outcome data but advocates for proceeding with male gender assignment in undervirilized DSD patients given the positive results of long-term follow-up in transsexuals undergoing reconstruction [66].

Late Presentation of the Undiagnosed DSD

While modern medical knowledge and diagnostic testing has led to increased recognition of DSD, there are still cases which evade diagnosis until adolescence or beyond. In a recent study on CAH, the rate of diagnosis for children under 12 months of age was 5.5 per 100,000 compared to 0.23 per 100,000 for those are 12 months to 15 years [79]. Cases of delayed diagnosis are more common in cases of 5αRD2, particularly in areas where definitive testing is less accessible [80]. In many cases, the recognition of a DSD condition is made following the diagnosis of a germ cell tumor [81]. In other cases, the diagnosis is made as a result of the recognition of specific anatomic abnormalities (e.g., hypospadias and cryptorchidism) or anatomy inconsistent with the sex of rearing [82–84]. It is also important to recognize the possibility of an incorrect DSD diagnosis. This inaccuracy can be present in up to 50 % of adult patients diagnosed as children with a higher rate of misdiagnosis in older individuals, presumably due to a relatively less complex understanding of DSD conditions at the time of diagnosis [85]. When the diagnosis is delayed, it is often more difficult for the individual to understand and accept the diagnosis [86].

Once an undiagnosed DSD is suspected, the process of investigation is essentially identical to that of the newborn identification, if the gonads have not been removed. In situations where gonadectomy has already been performed, it is considerably more difficult to make and confirm the underlying diagnosis [87]. One of the most worrisome risks in those with a late diagnosis of DSD is the possibility of a GCT having developed in a dysgenetic gonad. In these individuals, it is advisable to remove the gonad(s) as would have been recommended if the DSD was recognized in the newborn period. In cases, such as 5αRD2, where testicular malignancy is of little or no concern, orchidopexy needs to be performed.

Management of the genitalia is another prominent issue in those with late DSD diagnosis. In the case of an undervirilized male, planning to live as a male, there is often the need to manage complex, proximal hypospadias defects with the potential for more complications and increased likelihood of needing multiple procedures to achieve a successful outcome [57]. In all adult DSD populations, attempts at surgical reconstruction are often more challenging given that these operations are often revisions of earlier reconstructive attempts. Formation of scar tissue, adhesions, destruction of tissue planes, and altered anatomical relationships can all contribute to more complicated operations with a higher risk of postoperative complications.

When DSD patients are young, it is their parent(s) that need more emotional and psychological support. As the individual moves into adolescence and adulthood however, the focus of psychological support shifts toward the patient. The issues faced: gender identity, gender role, sexuality, sexual orientation, fertility, and understanding of diagnosis/surgical interventions, are complex and require an expert and multidisciplinary approach. In a variety of metrics, it has been shown that DSD patients have greater psychological issues than non-DSD patients [88]. Issues surrounding female sexuality are particularly problematic with differences seen in sexual activity, dyspareunia, and motivation [89]. Males also face significant psychosexual issues cosmesis, sexual performance, and general sexual activity [90]. Both males and females have the potential to experience gender dysphoria as they progress through adolescence/adulthood.

Some studies report very low rates of gender dysphoria [91] while others cite very high rates (38 %) in certain DSD populations [92]. A 2012 study by Furtado et al. reviewed much of the current literature on gender dysphoria in DSD, and report a rate of 8.5–20 %, with rates varying depending on the specific DSD condition [93]. In the era of multidisciplinary DSD teams, the role of the mental health provider is increasingly integral, both to the patient, but also as a facilitator between members of the care team and families [88].

As our understanding of the extreme complexity of DSD patients has evolved, multidisciplinary teams designed to help guide initial evaluation and follow-up management have become a standard in pediatric institutions. The emergence of these teams has led not only to enhanced medical and surgical care but has also been fundamental in establishing means to track and study the outcomes of these individuals as they progress through childhood and into adulthood. The complexity of these transition issues and suggestions for solutions is comprehensively outlined in a recent article by Crouch and Creighton [94]. As described, there often exists a void in the care of these individuals as they become adults. It can often be difficult for individuals to find adult providers willing and able to care for their unique medical needs. In addition, the care, which has often been provided by providers all located within a single medical center, frequently becomes fragmented between multiple medical institutions. This lack of a central care facility places a large burden on the patient in a variety of social and economic aspects. It also has the potential to fragment communication between providers unless there is a specific care provider willing to serve as a mediator between all parties.

Conclusion

Individuals with DSD are a challenging population with regard to diagnosis, management, and long-term care. As our ability to screen for, and identify, these conditions has improved it has been possible to provide definitive or near definitive management early in life. Unfortunately however, early management does not guarantee long-term outcomes, and thus it is imperative that there are resources in place to care for patients with DSD throughout their lifetime. In addition, it is important to recognize that individuals with DSD may not present until later in life and may present with the sequelae of their untreated condition (e.g., gonadal malignancy). An understanding of prioritization and multidisciplinary approach to the various aspects of the individual condition is extremely important and may require the expertise of adult and pediatric practitioners regardless of the patient's age. Finally, given that many of the treatment approaches and procedures performed today are relatively new, we must recognize that only time will reveal the true outcomes and comprehensive follow-up to facilitate a better understanding up our end results is essential.

Recommendations Summary

- Decisions about how to manage the gonad(s) in DSD patients need to consider the hormonal, reproductive, and oncologic implications of any intervention or observation strategy.
- The timing of and techniques for genital reconstruction remain heavily debated and should be discussed by specialized multidisciplinary DSD teams in concert with the family/patient.
- The management of a patient with a late diagnosis of a DSD condition needs to include all the components of standard management and recognize the potential for additional psychosocial complexity.

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The Adult Hypospadias Patient: Technical Challenges in Adulthood

8

Moneer K. Hanna and Gina M. Cambareri

Primary Hypospadias in Adults

Hypospadias repair is usually performed during early childhood; however, sometimes this anomaly is left untreated until adulthood and in the majority of these cases the meatus is distal. The degree of curvature may have been unappreciated by both the parents and the primary care physician, and this is also fairly common in developing countries. Although patients with marked chordee and a proximal meatus will be affected by the abnormality, the disability caused by mild variants of hypospadias is less obvious. Dodd's et al. 2008 [1] paper reported their experience with 56 adults and found that 18 (32 %) stated that they were not aware they had an abnormality of the penis. None of the 56 patients complained of voiding problems however 20 (36 %) stated when asked that they had spraying or angulation of their urinary stream. Most (95 %) of the adult patients in their series stated that they were satisfied with the appearance of their penis, whether or not this finding is attributable to patient denial/embarrassment, lack of insight about what normal is, or true satisfaction remains unclear. A survey of adults with uncorrected hypospadias involved a study of 500 consecutive men who underwent transurethral resection of the prostate or transurethral resection of bladder tumor. The investigators [2] reported that 13 % of their patients had anterior hypospadias. Sixty three percent of the patients were unaware that they had a genital anomaly, and none of them had voiding or cosmetic complaints.

The surgical techniques for the repair are similar to those used in children. Senkul et al. [3] reported on 88 adult patients with an average age of 21.9 years. The primary cases consisted of 48 anterior (7 glandular, 13 coronal, and 28 subcoronal), 9 midpenile, and 2 proximal hypospadias. They used the MAGPI repair in 14 patients, Mathieu repair in 36 and TIP repair in 5. Of the four remaining patients, one had an Asopa, one had a Duckett, one had a two-stage repair, and one buccal mucosa tube. They reported a complication rate of 10.1 % for the primary repair and 27.5 % for the secondary repairs. Another large series was reported by Adayener and Akyol in 2006 [4] included 97 adult patients (80 primary and 17 secondary). The meatal position was glandular in 6, coronal in 35, and subcoronal in 56 patients. The 97 surgeries involved 42 MAGPIs, 41 Mathieu, and 14 TIP procedures. 73/80 (91.4 %) primary repairs were successful; they observed that the success rate for primary adult

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cases was acceptable, but it was less in patients who had a longer neourethra.

Our experience in primary hypospadias is relatively small: 10/221 adolescents, 8 coronal, and 2 midpenile. We have used the Thiersch Duplay (TD) repair in all cases and encountered complications in two patients (20 %), where one developed a fistula and the other had glans dehiscence. This complication rate is much higher than our previously reported 2.1 % in 512 children [39] using the same technique (Fig. 8.1). A similar outcome was reported by Hensle et al. [5] with the use of the TD repair and Mathieu procedure. In their series 2/6 (33 %), adult patients developed urethral fistula and all were successfully repaired.

Li et al's [6] experience with the repair of hypospadias using a bladder mucosal tube in 113 adolescents and adults is remarkable. The ages ranged from 13 to 29 years (mean age was 17.1 years). There were 31 primary cases in which adequate foreskin was lacking and 82 secondary cases. The meatus was penile in 33, penoscrotal in 72, and perineal in 8. All of the repairs except one (primary or secondary) were performed as one-stage procedure. They achieved satisfactory cosmetic and functional results in 99 patients (87.6 %). Others have not replicated the success of bladder mucosal tubes, and this technique has been largely abandoned.

Secondary Hypospadias Repairs (Table 8.1)

Our approach for creating a neourethra in redo and complex hypospadias repair has evolved over three decades. We now have an experience with 203 hypospadias cripples who had had 2–23 surgical procedures prior to referral, 126 of whom were previously reported [7]. Early on we used tubed free skin grafts, then tubed bladder mucosa grafts, and later on buccal mucosal grafts and have incorporated any residual urethral plate if it appears healthy no matter how narrow it was. When we reviewed our complication rate for the tubed free skin grafts in 2005, it was 32 %, but rose to 54.5 % by 2010 as more of these grafts developed lichen sclerosis. Our experience with bladder mucosa is that it tends to proliferate in the presence of irritating factors. Accordingly, the most common complication involving all bladder mucosa substitution urethroplasties involves meatal stenosis. When the bladder mucosa is exposed to air, it becomes sticky, friable, and hypertrophic leading to meatal stenosis. Although this can be prevented by anastomosing a 1 cm full thickness skin graft to the distal end of the mucosal tube, the potential morbidity of the end-to-end anastomosis of two free grafts and the sclerosis of the skin tube makes this proposition unappealing.

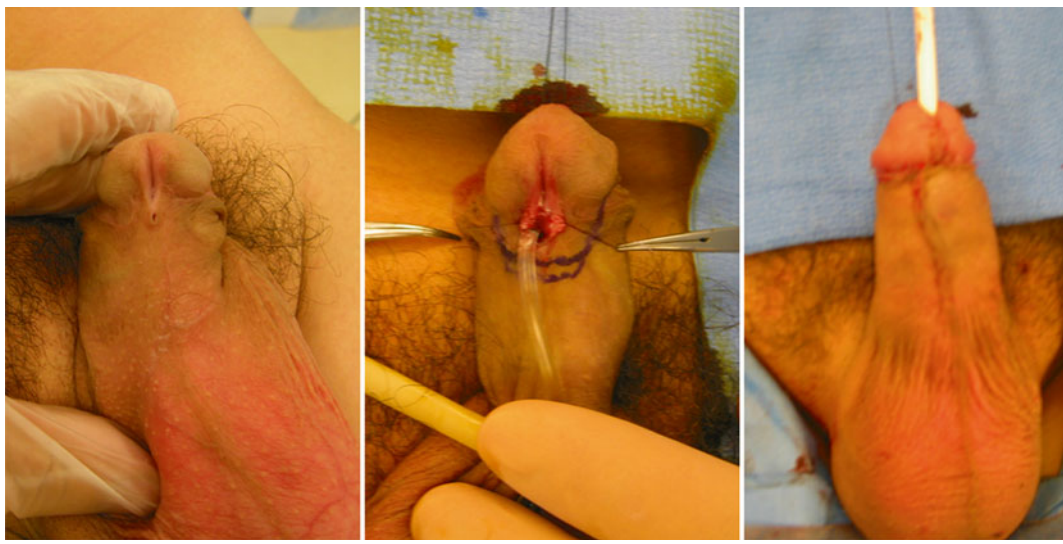

Fig. 8.1 Doral Heinke-Miculikz meatoplasty and Thiersch-Duplay repair for sub-coronal stenotic meatus and deep glans sulcus

Table 8.1 Primary and secondary hypospadias repair in adult and adolescent patients: review of the literature

	Patients (number)	Average age (years)	Follow-up	Primary repair (number)	Secondary repair (number)	Type of repair	Presenting complaint	Staged or single stage	Outcome (success rate)	Complications
Li et al. [6]	113	17.1 (13– 29)	3 months to 2 years	31	82	Tubularized bladder mucosa	Hypospadiac meatus	Single Stage	87.6 %	– UCF 7.1 % – Urethral stricture 5.3 %
Hensle et al. [5]	42	22.5 (18– 47)	1– 19 years	8	34	– Primary: Thiersch-Duplay, Mathieu, Island pedicle tube graft – Secondary: Fistula closure, Mathieu, Island pedicle tube graft, buccal mucosa tube graft, Island pedicle onlay graft, bladder mucosa tube graft, buccal mucosal onlay graft, split thickness skin graft	– Hypospadias meatus – Chordee – UCF – Scarring – Hair bearing urethra – Urethral stones – Diverticulum	Single	– 62.5 % in primary stage repairs – 44.1 % in secondary stage (36.3 % in “cripples”) – Outcomes increased to 100 % primary repair after secondary surgery and 85.3 % in secondary surgery	– UCF 10 – Stricture 6 – Graft loss 2 – Graft contracture 2 – Skin flap loss 2
Senkul et al. [3]	88	21.9 (20– 27)	28 months (5– 60 months)	59	29	– Primary: MAGPI, Mathieu, TIP, Asopa, Duckett, two stage, buccal tube – Secondary: fistula, Mathieu, TIP, in situ tubularization, buccal tube, and onlay	– Primary: hypospadiac meatus – Secondary: UCF, hypospadiac meatus, cripple	Both (only 2 staged)	– 89.9 % in primary – 72.5 % in secondary – After secondary interventions increased to 100 % and 89.6 %	– Primary: fistula, partial graft loss – Secondary: fistula, partial graft loss, total graft loss, stricture
Snodgrass et al. [33]	25	18 (16 months– – 40 years)	5 months (6 weeks– 14 months)		25	Bracka two-stage repair with buccal mucosa	Scarred urethral plate and residual hypospadias	Staged	65 % (in 20 patients)	UCF, glans dehiscence

(continued)

Table 8.1 (continued)

	Patients (number)	Average age (years)	Follow-up	Primary repair (number)	Secondary repair (number)	Type of repair	Presenting complaint	Staged or single stage	Outcome (success rate)	Complications
Amukele et al. [7]	126	14 months–35 years	12 months		126	Free skin, bladder and buccal grafts, Thiersch-Duplay	Hypospadias cripples, chordee	Single Both	74 % 79 %	Multiple UCF, stricture, skin tethering, breakdown, inclusion cyst
Dodson et al. [34]	31	13 (10–62)	14 months (1–288)	31	n/a	Metal-based flaps, MAGPI, island onlay flaps, staged procedure, TIP, tube graft, Mathieu	Hypospadiac meatus	Both	52 %	UCF, stricture, hematoma, loss of repair, urethral web
Sharma [35]	13	18–26	0.5 years (0.25–3)	13	n/a	TIP urethroplasty	Hypospadiac meatus	Single	76.9 %	UCF (closed spontaneously)
Hatipoglu et al. [36]	27	22	13 months (6–18)	27	n/a	TIP urethroplasty	Hypospadiac meatus	Single	81.4 %	Meatal stenosis (successfully dilated in all) and UCF (closed at 6 months)
Adayener and Akyol [4]	97	21.8 (20–26)	19 months (6–31)	80	17	MAGPI, Mathieu, TIP urethroplasty	Hypospadiac meatus	Single	– Primary 76.5 % (increased 100 % secondary procedure – Secondary 91.3 % (increased 100 % in secondary procedure)	– Primary: UCF, skin flap loss – Secondary: UCF and flap loss

Barbagli et al. [37]	60	32.2 (19–37)	33.8 months (12–138)	n/a	60	Meatoplasty, anastomotic repair, fistula closure, dorsal inlay graft or flap with skin, buccal mucosa inlay and onlay, multistage with skin, multistage with buccal mucosa	Urethral stricture, residual hypospadias, UCF, meatal stenosis, penile curvature, hair, diverticular, stone	Both	75 % (different success based on one stage vs. multi stage and source of graft)	UCF, meatal stenosis, glans dehiscence, poor cosmesis, residual chordee
Barbagli et al. [38]	1,176	31 years (1–76)	60.4 months (12–137)	1,176	n/a	Meatoplasty, UCF closure, end-to-end anastomosis, perineal urethrostomy, buccal mucosa, skin graft or flap, Johanson, glans reconstruction, penile skin reconstruction, corporoplasty	Urethral stricture, residual hypospadias, UCF< meatal stenosis, residual curvature, hair, diverticula, stones	Both	88.1 %	Types of complications not reported
Schwentner et al. [39]	31	13.5 (15 m–26 years)	78.45 months (61– 116 months)	n/a	31	Single stage full thickness genital skin grafts	UCF, urethral stricture, residual hypospadias, diverticula or breakdown and all patients had a scarred urethral plate requiring graft	Single	87.1 %	Urethral stricture and fistula

(continued)

Table 8.1 (continued)

	Patients (number)	Average age (years)	Follow-up	Primary repair (number)	Secondary repair (number)	Type of repair	Presenting complaint	Staged or single stage	Outcome (success rate)	Complications
Lumen et al. [40]	25	36.2 (19–55)	45.4 months (4–92)	n/a	25	Free grafts, anastomotic repair, combined urethroplasty, pedicled flap, and staged repair	Urethral stricture	Both	72 % (fistula was not considered failure and not reported as failures)	– Recurrence of stricture – 4 patients with fistula, not reported as part of complications
Meeks et al. [41]	15	30.5 (18–57)	23 months (5–62)	n/a	15	Staged repair with grafts including buccal mucosa, auricular, abdominal skin, and penile skin	Lower urinary tract symptoms, infertility, chordee, fistula, hair, stone, and recurrent infections	Staged	86 %	Dehiscence, breakdown, fistula, poor cosmesis, coronal meatus, spraying, retention, buccal mucosa oral graft complications, UTI
Myers et al. [42]	50	38 (19–71)	89 months (median, range 6–198)	n/a	50	Penile skin flap, perineal urethrostomy, excision and primary anastomosis, tubularized plate, buccal mucosa onlay, UCF closure, chordee correction, combined	Urethral stricture, fistula, persistent hypospadias, hair in the urethra and chordee	Both	76 % (50 % initially)	Urethral stricture, UCF, periurethral infection, graft contracture, erosion
Cambareri and Hanna [39]	29	10–29	2 years in all (14 patients had follow-up 5 years)	n/a	29	Island skin flap onlay or buccal mucosal graft onlay	Urethral stricture in all, UCF, chordee	Single	86.2 % (increased to 93.1 % with secondary procedures)	UCF and recurrence of stricture

Furthermore, the pliability of bladder mucosa also leads to ballooning during voiding and over time diverticulum formation. We have reported 27 bladder mucosal tubed grafts in complex hypospadias cases [7] and encountered 6 major complications (2 strictures, 3 mucosal prolapse, and 1 fistula with mucosal prolapse). There were four patients who developed minor complications (skin tethering in three and inclusion cyst in one). A consistent problem has been exuberant overgrowth of transitional epithelium at the meatus producing a "cauliflower like "appearance. The total of 37 % secondary surgeries following bladder mucosal tube in our patients and the additional surgery for harvesting the graft led us to abandon the bladder mucosa in favor of buccal mucosal grafts, as have others.

The popularization of oral mucosa-free grafts (OMG) in repair of hypospadias cripples has revolutionized treatment for this group [8]. When tissue transfer is needed, OMG is universally accepted as the best free graft due to ease of harvest, quality of substrate for urethral substitution, low late complication rate, and low long-term donor site morbidity [9, 10]. One-stage onlay or two-stage repairs are preferable to one-stage tubed repairs, resulting in lower complications with durable results in peripubertal/postpubertal patients [2, 11–16, 33]. Successful outcomes in postpubertal hypospadias cripples are more difficult to achieve than in a prepubertal population, rendering a need to utilize two-stage approaches for peri- and postpubertal hypospadias cripples [37, 41]. Urinary function, as characterized by AUA-SS, for patients undergoing buccal mucosa graft reconstruction is reasonable, with most patients reporting mild LUTS. Even after successful repair, however, cosmesis continues to be a challenge for this group, with 1/3 of patients undergoing OMG reconstruction stating that they are very or somewhat dissatisfied with the cosmetic outcome [17]. Sexual function in this group of patients has been characterized utilizing the IIEF and demonstrating excellent results. Similar to all hypospadias patients, ejaculatory complaints predominate [17].

Urethral Fistula

Fistula is an ingrowth of epithelial cells along the suture tracts, and when large is a localized tissue necrosis. Small fistulas may present at a later date during adolescence. After ruling out distal obstruction, closure of a simple fistula can be achieved by dissecting out the fistula tract and directly approximating the edges without narrowing the urethral lumen followed by intraoperative testing for water tightness of the closure, waterproofing by a Dartos or tunica vaginalis flap, and coverage with a rotation trapdoor skin flap based on the upstream edge (Fig. 8.2). Complex fistulae including large, multiple, and

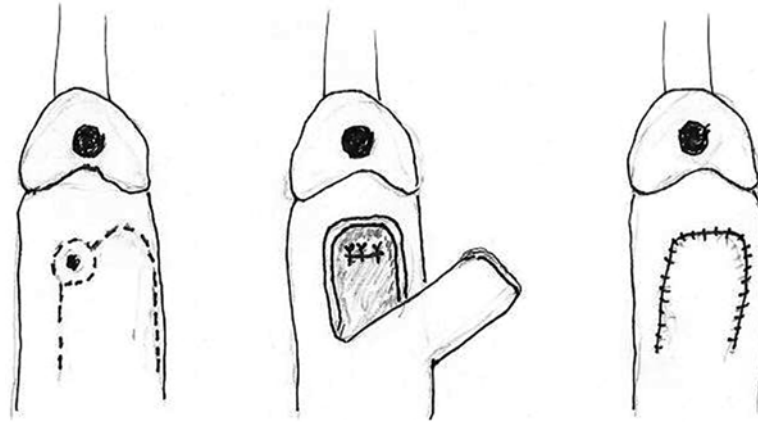

Fig. 8.2 Closure of a simple fistula

recurrent may be a manifestation of another problem. Richter et al. [18] reviewed the records of 28 patients, who had had between 2 and 15 attempts at closure where 17 had a single fistula and 11 patients multiple fistulae were present. The causes of failure were believed to be the awkward fistula site in 12 (coronal fistulas), urethral diverticulum in 7, and distal urethral stricture in 4. In 5 patients, the cause of the recurrent fistula was unclear. In these cases, intraoperative calibration of the distal urethra and urethral distension using a syringe full of water and a Christmas tree adapter will demonstrate a stricture or a diverticulum.

For larger fistulas where direct closure would narrow the urethral lumen, either a lateral hinge flap or an adjacent skin flap on subcutaneous mesentery (island flap) can be used. If the local skin is scarred, a free-patch graft of buccal mucosa with buttressing by a tunica vaginalis flap would be another surgical option.

Coronal fistulas are notoriously difficult to repair by layered closure because the distal glandular tissue is fixed. This often causes some degree of tension on the suture line, hence the high failure rate of coronal fistula repairs. In our experience, coronal fistulas are best repaired by converting them to coronal hypospadias, by dividing the bridge of tissue between the fistula and meatus. Then, the urethral plate is tubularized using a wider strip (Thiersch-Duplay tube) with or without a dorsal midline relaxing incision depending on how deep the glans sulcus is (Fig. 8.3). In resurfacing the operative site, the traditional transposition flaps (Y-V and advancement) may be unreliable because their vascularity may have been compromised by previous surgery. The hairless midline scrotal island or rotation of a scrotal flap is more reliable for these cases. It should be noted that these are random flaps and a width/length ratio of at least 1:2 should be maintained.

Chordee

The residual or recurrent curvature, apart from the obvious deformity, may interfere with sexual intercourse. It may be due to incomplete correction during the primary childhood repair or due to recurrent fibrosis secondary to previous operative

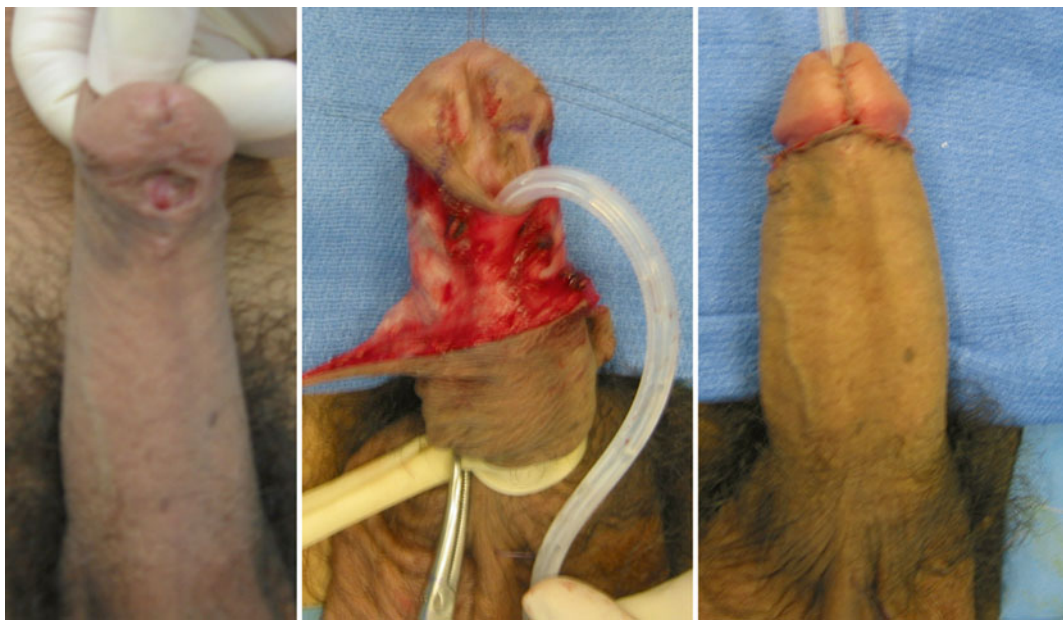

Fig 8.3 Large sub-coronal fistula: division of glans bridge and distal redo T-D urethroplasty

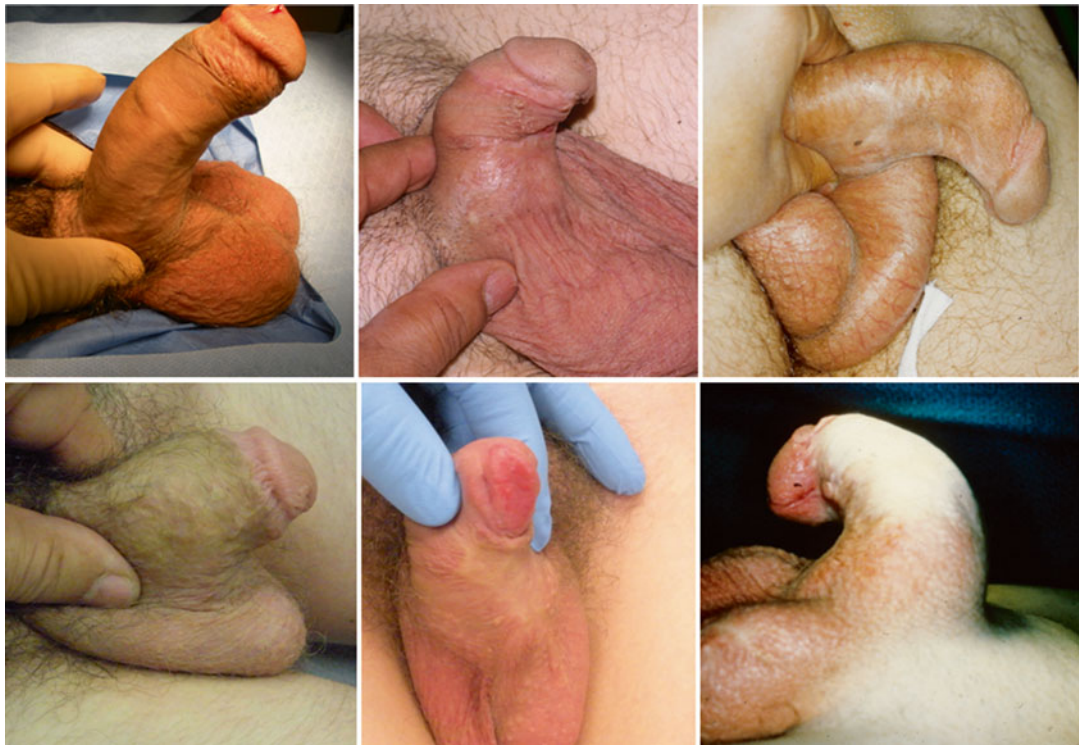

Fig. 8.4 Spectrum of mild to severe ventral residual and recurrent chordee. Aesthetic-functional disability

trauma. In our experience, penile curvature was present in 76/221 adults and the spectrum of the curvature varied from an aesthetic nuisance to functional disability (Fig. 8.4). It is necessary to take a careful sexual history for all postpubertal patients with planned operative repair of a urethral complication to ensure that chordee can be addressed simultaneously if problematic.

The role of an intraoperative artificial erection to assess the adequacy of the chordee release has been repeatedly stressed. Gershbaum et al. [19] reported the long-term follow-up for surgical repair of severe chordee associated with perineoscrotal hypospadias in 34 patients. There were two groups of patients: the first group of 23 children underwent one-stage repair, and the chordee was repaired by a dorsal shortening procedure (Nesbitt repair or tunica albuginea plication). The second group of 11 children had two-stage repairs and the chordee was corrected by a ventral corporal lengthening with either a dermal or tunica vaginalis free graft. At 5–15-year follow-up recurrent chordee was noted in 5/23 (21.7 %) in group 1 (dorsal shortening) and there was no recurrent curvature in the second group (ventral grafting)

The first step in repairing recurrent or persistent curvature in adolescent and adults is the degloving of the penis and radical excision of all scar tissue, then induction of an artificial erection, if the curvature is relatively mild (30° or less) the modified Nesbitt procedure [20] (Fig. 8.5) or the simpler Baskin modification [21] (Fig. 8.6) should straighten the penis. When the curvature is severe due to corporal disproportion or severe scarring (Fig. 8.7), it would be wiser to avoid dorsal shortening procedures and opt for a two-stage repair. In stage 1, an autologous dermal or vein graft or off-the-shelf transgenic alternative can be used to correct the curvature and lengthen the ventral corporal wall and then covered with a well-vascularized skin flap (Fig. 8.8).

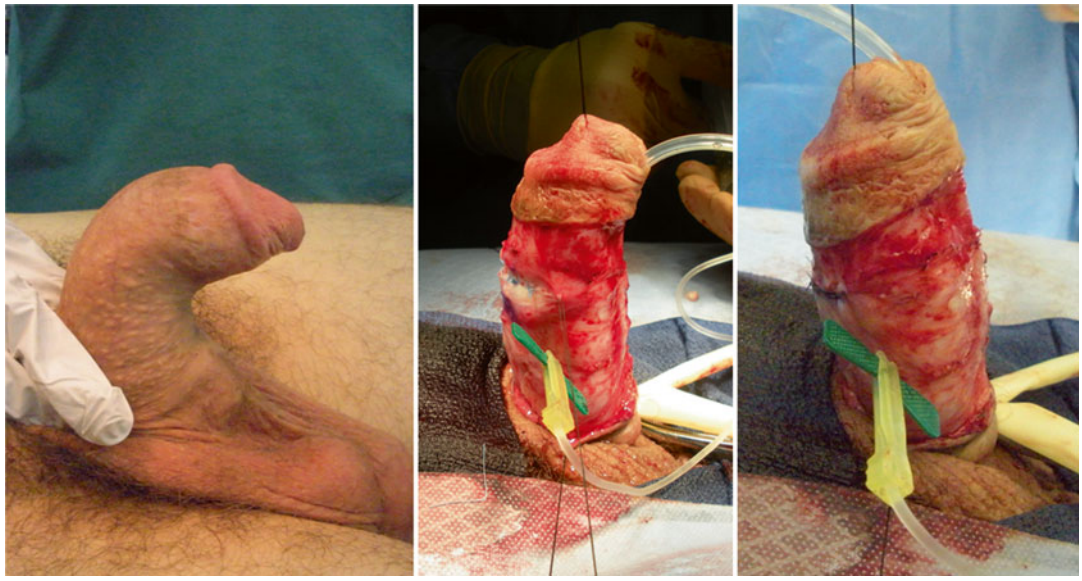

Fig. 8.5 Curvature partly scarring and partly corporal disproportion: Nesbitt Repair

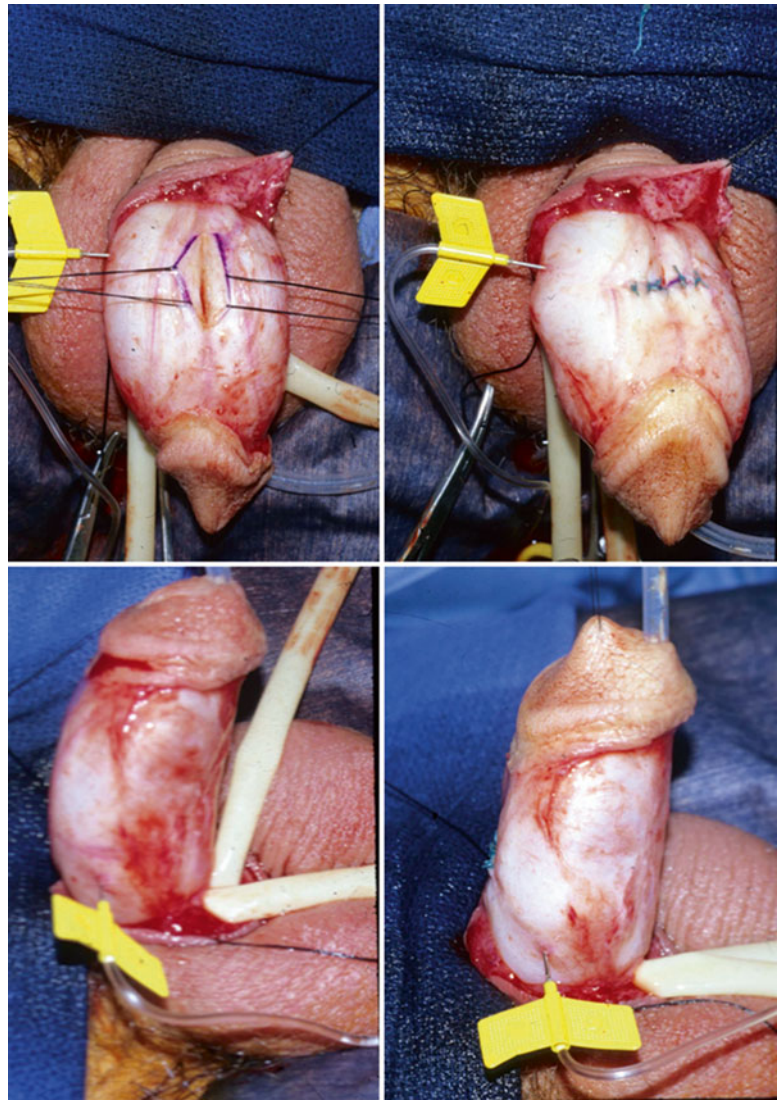

Fig. 8.6 *Top*: Modified Baskin chordee repair. *Bottom*: Artificial erection test, pre- (*left*) and post-repair (*right*)

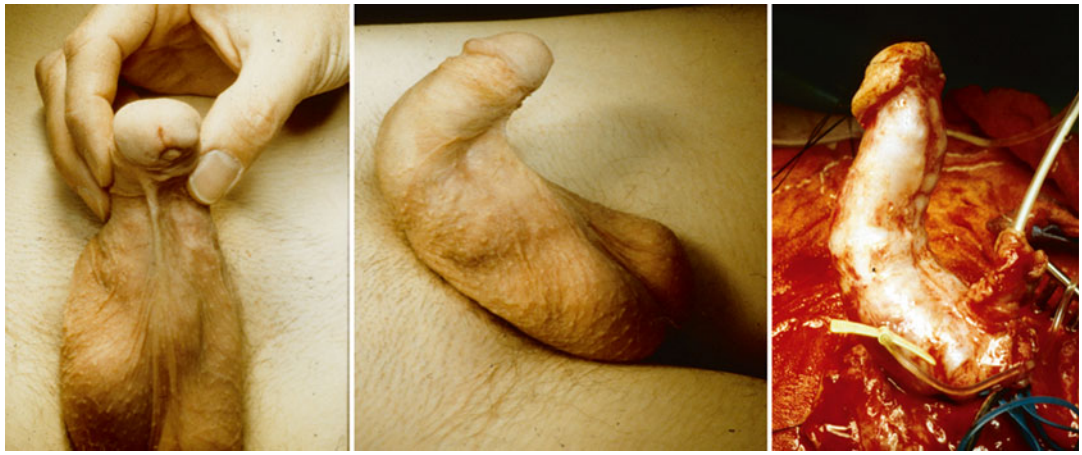

Fig. 8.7 Residual chordee post hypospadias repair due to corporal disproportion

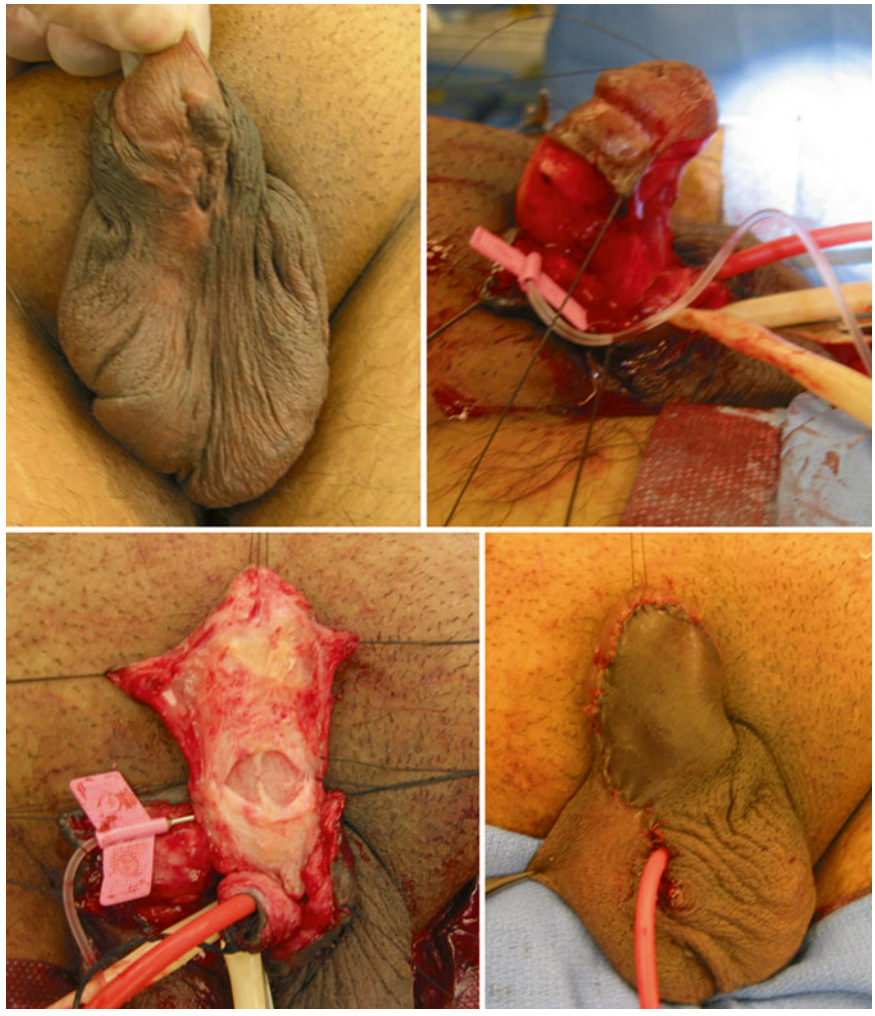

Fig. 8.8 A 29-year-old patient, who had 14 operations. *Stage I*: excision of scarred plate, ventral corporal lengthening by a dermal graft, and coverage with a side flap

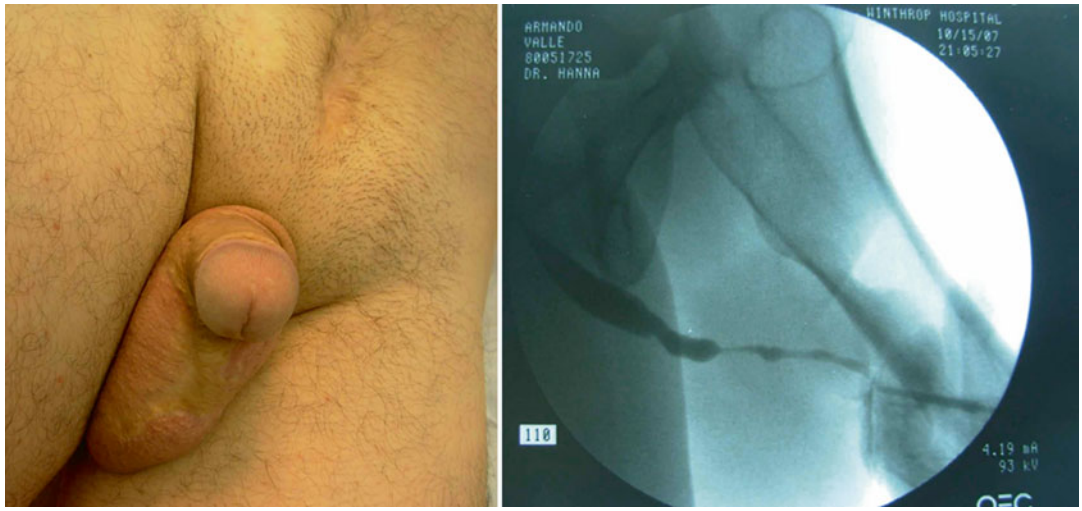

Fig. 8.9 A 36-year-old patient, who had two-stage hypospadias repair at 2 years of age, and later voiding symptoms at 29 years of age. Long urethral stricture (8FR) with relatively healthy urethral plate

Stricture

Urethral strictures following hypospadias repair are fundamentally different from those secondary to inflammatory disease or post-trauma. The bulbospongiosum tissue is lacking, and the stricture may appear many years and even decades after the surgery (Fig. 8.9). The exact incidence is unknown. In men who present with urethral stricture, complications of previous hypospadias repair such as urethral fistula and or persistent curvature are common. Lumen et al. [22] reported the leading cause of iatrogenic urethral stricture in men younger than 45 years was due to prior hypospadias repair. Greenwell et al. [23] described the evolution of urethroplasty for urethral strictures. For long stricture of the penile urethra, some form of substitution urethroplasty is necessary. While some advocate a one-stage operation, adult reconstructionists typically favor a two-stage approach for penile urethral reconstruction using OMG. To date, no studies definitely support one-stage vs. two-stage approaches. In general, tubed flaps or grafts do not do well even in the hands of experienced surgeons. We have abandoned the use of a one-stage mucosal tube in favor of a patch graft, as they tend to result in fewer failures, likely due to improved acquisition of a new blood supply. The process of angiogenesis appears to be less efficient for a circumferential large surface area (tube) than a somewhat localized flat patch.

The management of urethral stricture disease following hypospadias repair is still controversial. In patients with a scarred or deficient urethral plate and/or concomitant lichen sclerosis (LS) (Fig. 8.10), a staged repair is recommended. When oral mucosa is used in a two-stage repair for a scarred urethral plate, one would expect to revise the graft in 10–15 %, as the recipient bed was abnormal to begin with (Fig. 8.11). For patients who have a healthy residual urethral plate, regardless of its width, either a single stage onlay or inlay buccal mucosal graft or a local island skin flap [24] can be used. The decision for either technique should be based on the quality of the penile skin and surgeon's preference. Some surgeons favor dorsal inlay over ventral onlay of buccal mucosa grafts. There are valid arguments for the dorsal placement of the graft (i.e., better support and fixation to the corpora cavernosa resulting in less sacculation), which may result in less post-micturition dribbling. However, ventral onlay is easier to perform, and still advocated by some.

Endoscopic treatment by optical internal urethrotomy of urethral stricture for patients without

hypospadias surgery has been reported to be very successful when the stricture is confined to the bulbar urethra [25]. However, the same treatment is less successful after hypospadias repair. Scherz et al. [26] reviewed 34 cases who developed a stricture following hypospadias repair and were classified into those with early (<3 months) and late strictures (>3 months). Manipulative therapy, which included urethral dilation and internal urethrotomy, was successful in 46 % of early and 16 % of late strictures. Patients who went onto open surgical repair ultimately had 82 % success. Another study of 38 patients with urethral stricture after hypospadias repair presented with voiding difficulties at a mean of 27.5 months. These patients were gleaned from 582 hypospadias repairs (6.5 %) and were retrospectively reviewed. A total of 29 patients underwent urethrotomy or dilation as their initial treatment with 79 % requiring urethroplasty due to failure of endoscopic treatment [27].

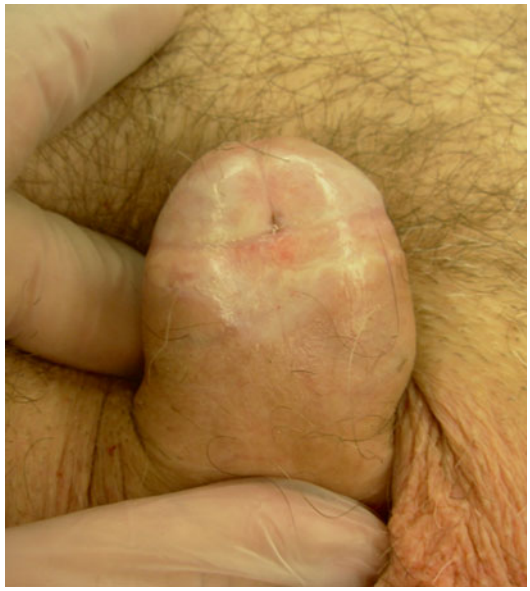

Fig. 8.10 Balanitis xerotica obliterans. Characterized by an insidious onset, dense ivory fibrosis, hyperkeratosis, atrophic dermatitis thin rete pegs, dermal collagen forming a homogenous band, deep infiltration of inflammatory cells

Husmann et al. [28] conducted a comprehensive review of the direct vision urethrotomy for short (less than 1 cm) penile urethral strictures following hypospadias surgery. Patients with short strictures located proximal to the meatus underwent internal urethrotomy. Based on the type of initial urethroplasty, patients were randomly divided into treatment with direct vision urethrotomy vs. direct

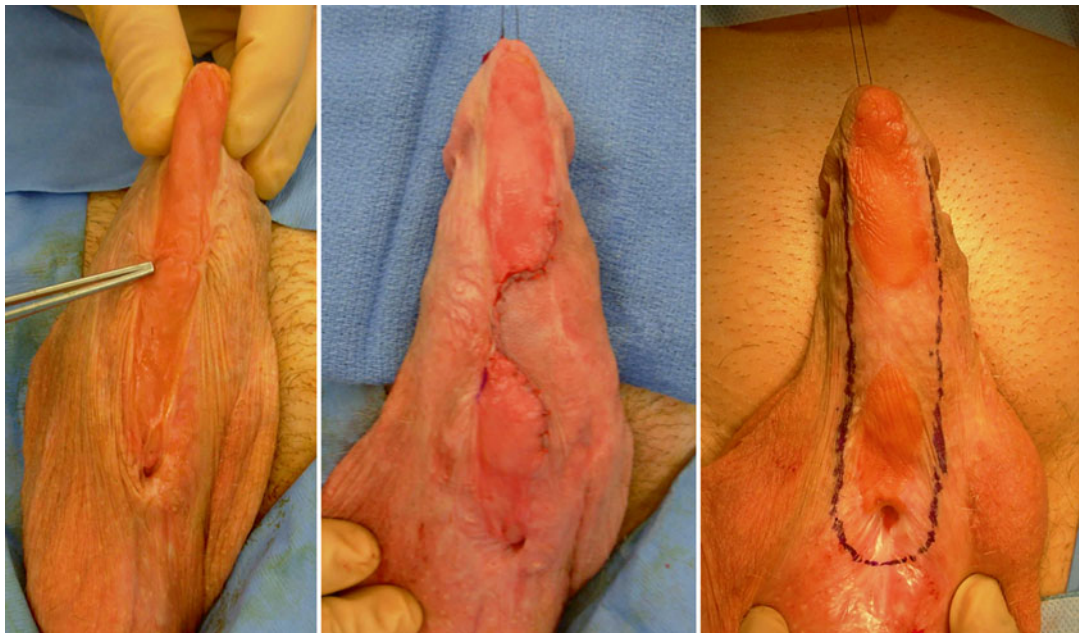

Fig. 8.11 Mucosal graft revision using skin if no BXO or another mucosal graft prior to tubularization

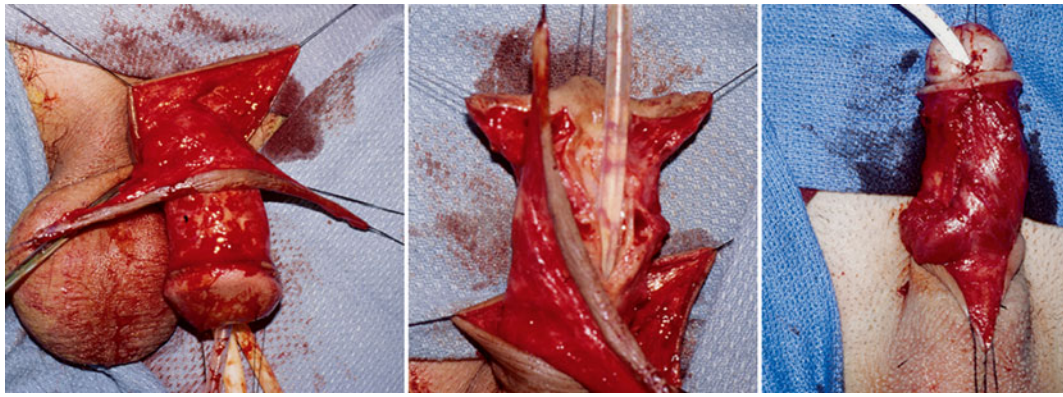

Fig. 8.12 Penile skin onlay urethroplasty

vision urethrotomy plus clean intermittent catheterization for 3 months. Success was defined as absent obstructive voiding symptoms and a normal urine flow 2 years following the last patient instrumentation. Of patients with urethral strictures following hypospadias repair 44 % (32) had previously undergone tubularized graft urethroplasty and 56 % (40) had previously undergone flap urethroplasty, including a tubularized island flap in 18, an onlay flap in 11, and urethral plate urethroplasty in 11. Direct vision urethrotomy alone was performed in 51 % of patients (37), and direct vision urethrotomy and clean intermittent catheterization were performed in 49 % (35). Success with the two methods was similar, that is, 24 % (9 of 37 patients) vs. 22 % (8 of 35). Following direct vision urethrotomy, all patients with tubularized graft urethroplasty showed failure (0 of 32). Success was noted in 11 % of patients (2 of 18) with tubularized island flap urethroplasty compared to 72 % (8 of 11) with onlay urethroplasty and 63 % (7 of 11) with urethral plate urethroplasty (each $p<0.05$). The authors concluded that the addition of clean intermittent catheterization to direct vision urethrotomy does not improve the likelihood of success. Direct vision urethrotomy for short (less than 1 cm) urethral stricture usually fails following any type of tubularized graft or flap urethroplasty, but it had moderate success following onlay flap and urethral plate urethroplasties.

Our experience [29] consisted of 29 patients with urethral stricture who had undergone previous hypospadias repair and retained a healthy urethral plate. Single stage urethroplasty using an island skin flap onlay in 14 patients (group1), where the penile skin appeared healthy with no scarring (Fig. 8.12) and buccal mucosa as an onlay graft in 15 patients (group 2). In all cases, the urethral plate was intact but narrow. The mean length of the urethral stricture was 7.1 cm (range 3–10 cm) in group 1 and 7.5 cm (range 2–12 cm) in group 2 (Fig. 8.13). Chordee was present and corrected in 7 patients in group 1 and in 11 patients in group 2. 19/29 of the patients had an associated urethral fistula. A successful outcome was achieved in 85.8 % in group 1 and 86.7 % in group 2 at a minimum of 2 years and the follow-up in 14 patients was 5 years (Table 8.2)

Table 8.2 Complications after secondary repair after hypospadias correction with salvageable urethral plate. Personal experience

Repair type	Island skin flap onlay ($N=14$)	Oral mucosa graft onlay ($N=15$)
Length	3–10 cm (mean 7.1)	2–12 cm (mean 7.5)
Fistula	1 (7 %)	1 (7 %)
Recurrent stricture	1 (7 %)	1 (7 %)
Urethral diverticulum	0	0

Hairy Urethra

While it is now recognized that non-hair-bearing skin (prepuce, urethral plate, or OMG) provides the best substrate for urethral substitution, historical

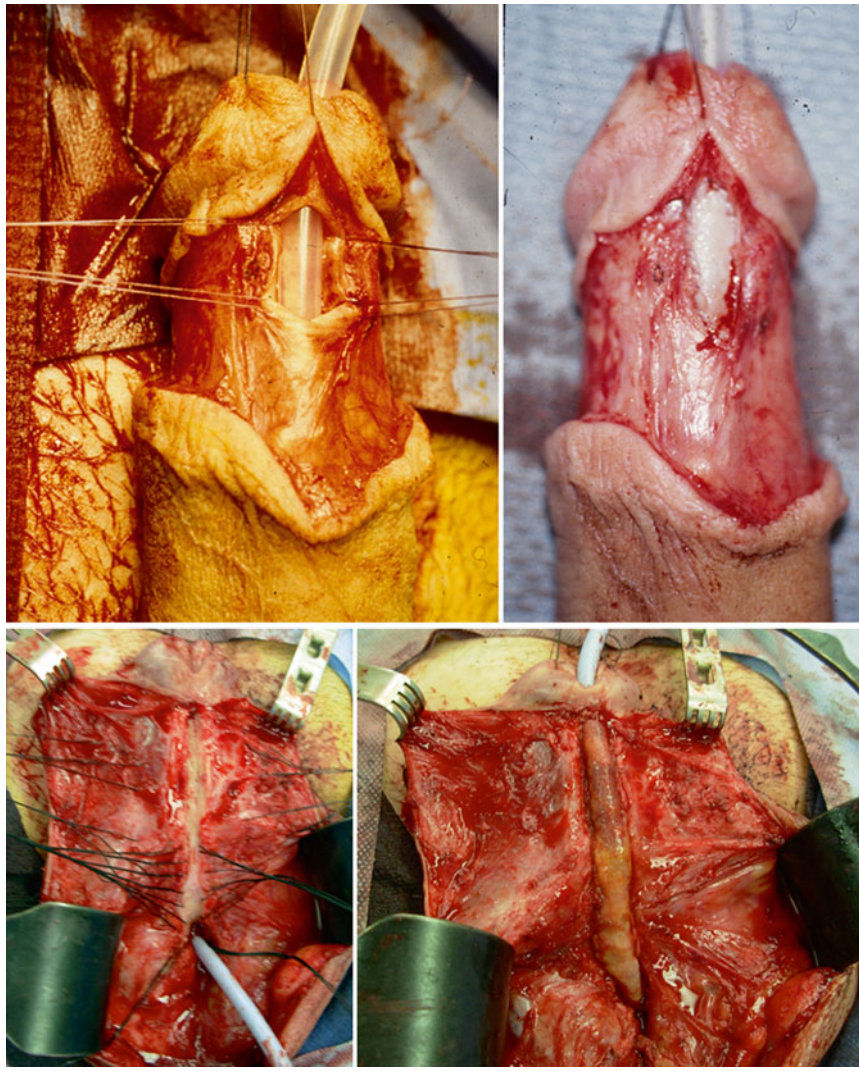

Fig. 8.13 *Top*: 2.5 cm buccal mucosa grafting of residual narrowed urethral plate *Bottom*: 12 cm buccal mucosa onlay graft

repairs often utilized scrotal inlay techniques which often result in hair growth and secondary stone formation in the urethra (Fig. 8.14). When only a few hairs are present, and there is no stone formation, this complication may go unnoticed and may cause no problems. However, in some hirsute patients the hair may grow and can be seen protruding through the urinary meatus (urethral beard). When a considerable amount of hair is present, recurrent pyuria, bacteriuria, and even stone formation, which can lead to urinary retention, may complicate matters (Fig. 8.15). We have found transurethral laser depilation is ineffective and have had to remove hairy urethras in five patients and replace them with a one-stage buccal mucosal patch in three- and two-stage urethroplasty in the other two patients.

Penile Skin Coverage

In redo and complex hypospadias repairs, and more so in hypospadias cripples, resurfacing of the penis can be problematic. It may be accomplished

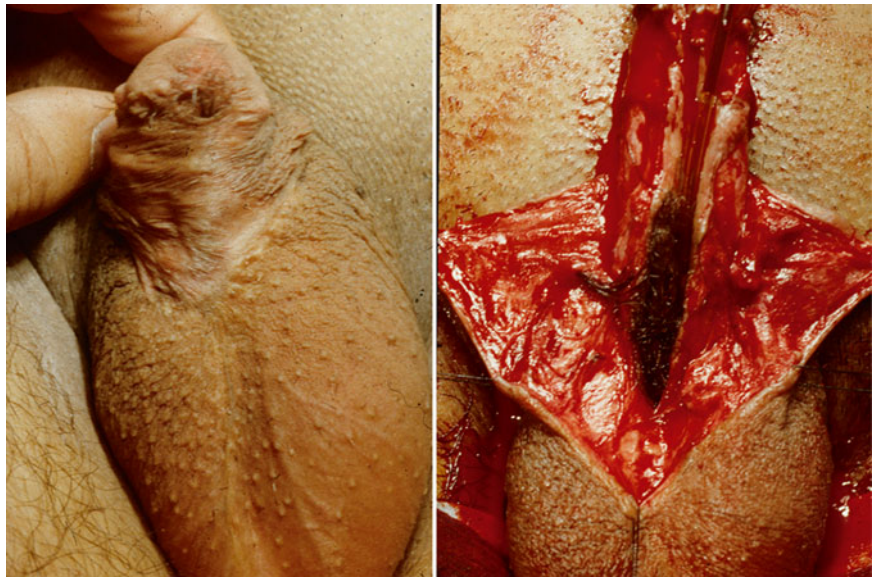

Fig. 8.14 Hairy urethra post hypospadias repair

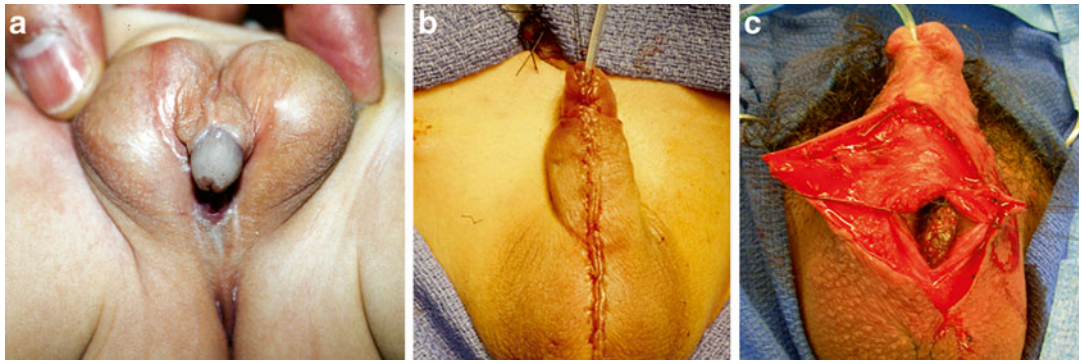

Fig. 8.15 (**a**) Perineo-scrotal hypospadias, (**b**) following two-stage repair, (**c**) acute urinary retention due to stone formation in a hairy urethra at 18 years of age

by local tissue rearrangement, such as a dorsal relaxing incision (Fig. 8.16), Z-plasty, rotation of a scrotal flap or burying the penis in the scrotum as described by Cecil [30]. An alternative for skin coverage involves skin grafts from extragenital areas. However, this option may result in different pigmentation (Fig. 8.17), and it may also lack sensation. Furthermore, extragenital skin grafts may result in significant complications, including graft loss with secondary scarring and chordee, graft shrinkage, and donor site morbidity. The grafted area is also insensate, which may promote sexual dysfunction.

We have used a scrotal fascio-cutanous rotational flap in 47 out of 193 complex hypospadias repairs (Fig. 8.18) and have found this flap to be reliable in 45/47 (95.7 %) of the cases [31]. In two patients, the distal end of the flap became necrotic and the distal urethroplasty dehisced. However long-term morbidity included revision of the flap in 10/43 (23 %) patients because of late scarring (4), excision of dog ear (4), and use of tissue expanders (2) for correction of iatrogenic penoscrotal webbing and aesthetic concerns. Depilation of hair was performed in 6 patients. In a series of 6 hypospadias cripples,

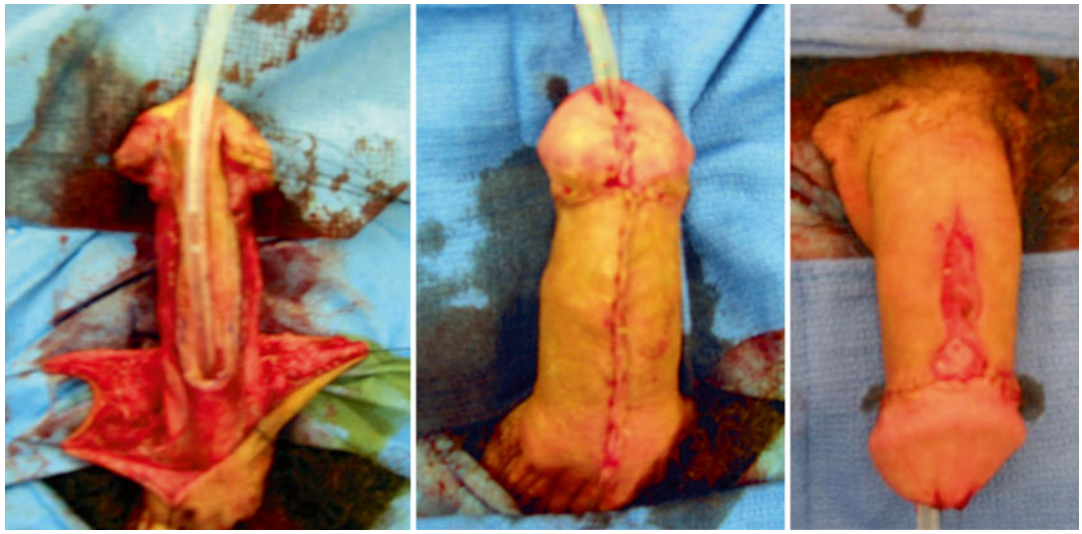

Fig. 8.16 Urethroplasty and dorsal relaxing incision

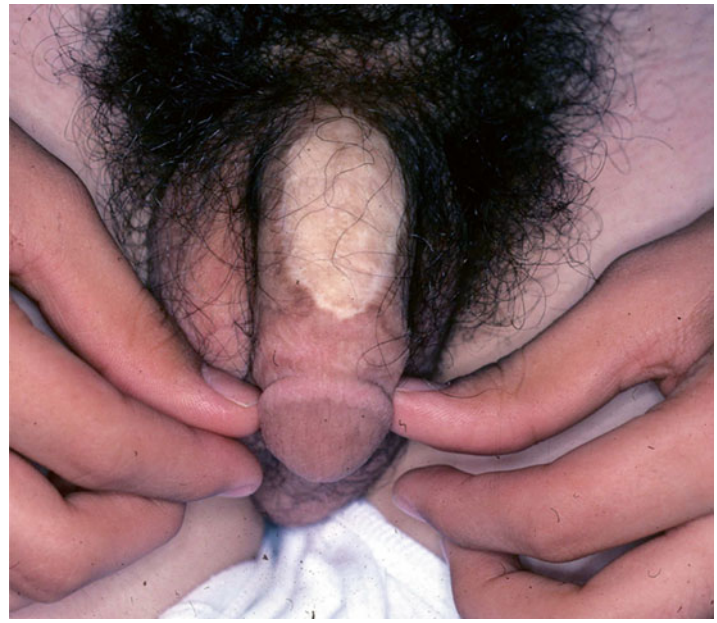

Fig. 8.17 Mismatched skin graft

Mir et al. [32] used tissue expanders successfully in all patients with a long-term follow-up to 22 years (mean 12 years) and success was measured by the following criteria: construction of a straight penis without curvature, a meatus in the glans penis at or near the tip, a urethra of adequate size, normal voiding, and acceptable cosmesis (Fig. 8.19). The two minor complications were a small fistula in one and meatal stenosis in the other patient, both unrelated to the use of tissue expanders. The local expansion of penile skin provides additional skin that is of perfect texture and pigment match and another additional theoretical advantage is that tissue expansion recruits additional skin with similar distribution of androgen receptors.

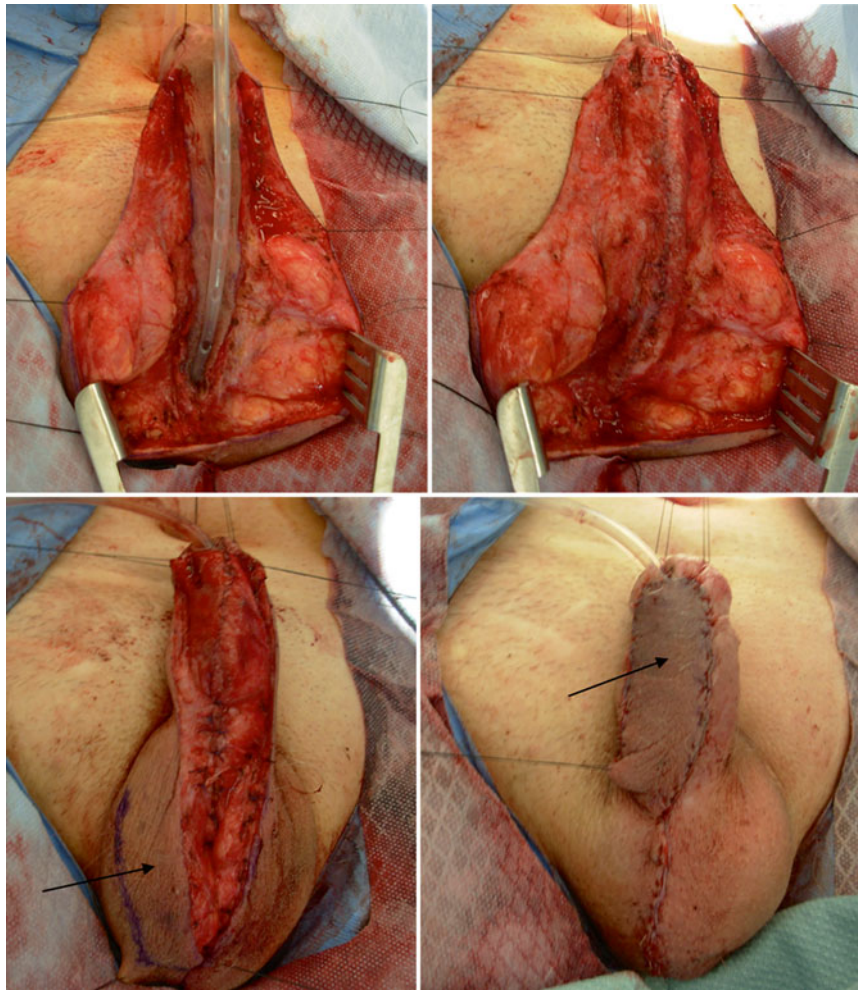

Fig. 8.18 Second-stage urethroplasty, waterproofing, and coverage by rotation of scrotal faschio-cutaneous flap

Summary

Primary hypospadias repair after adolescence is feasible, but subject to higher complication rates compared with repairs in childhood. Reported complication rates after primary repair in adulthood are 10–30 %, with urethral fistula being most common.

Repair of secondary complications in adulthood present a special technical challenge and are subject to complication rates ranging from 35 to 75 %, particularly for the "hypospadias cripple," who presents with penile scarring and a dearth of tissue for repair.

Flap onlay repairs and oral mucosa onlay grafts demonstrate the lowest complication rates in this group. A two-stage repair may be necessary when the urethral plate is deficient.

Tubed grafts demonstrate poor outcomes and should be avoided.

Complications encountered in adulthood include: recurrent stricture, urethral fistula, chordee, hairy urethra, and penile scarring or a combination of these.

Surgical planning should take into account the availability of native tissue and/or consideration of tissue supplementation with free grafts or local flaps if necessary for the most severely affected individuals.

Endoscopic management is less successful after hypospadias repair compared with patients with native urethral strictures, and probably only appropriate for short anastomotic strictures.

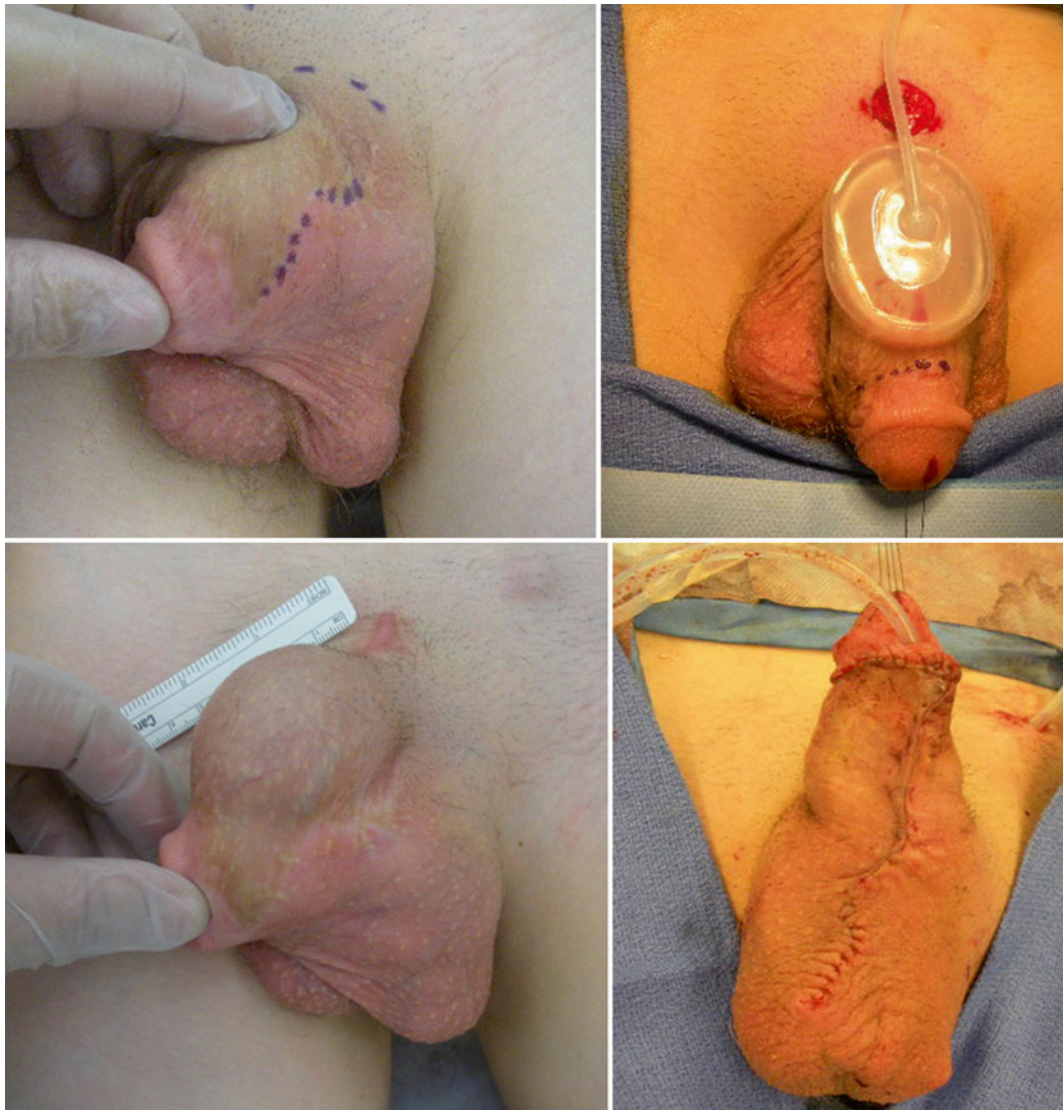

Fig. 8.19 Latrogenic penoscrotal webbing, placement of tissue expander, and subsequent repair

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Part III

Lower Tract

Urinary Tract Infections in the Reconstructed Bladder: Evaluation and Treatment Options

9

Vera Trofimenko, William O. Brant, James Hotaling, and Jeremy B. Myers

Introduction

Patients with neurogenic and reconstructed bladders have significant compromise of the innate defense mechanisms that prevent urinary tract infections (UTIs) in the normal human bladder, including the mechanical flushing of urine, cell-mediated immunity, secretion of immunoglobulins, and a protective mucous lining. Additional factors that contribute to UTI in this population include the formation of biofilms associated with the presence of indwelling catheters, congenital or secondary vesicoureteral reflux (VUR), large post void residuals, high-pressure voiding, and detrusor sphincter dyssynergia. In this setting, pathogenic organisms colonizing the bladder, introitus, or peri-stomal skin as in the case of reconstructed bladders can result in ascending infection that can lead to stone formation, acute pyelonephritis, sepsis, and renal failure [1]. While mortality related to urological problems has decreased dramatically since the early and mid-twentieth century, when 80 % of spinal cord injury (SCI) patients died from pyelonephritis, urinary tract problems remain the most common reason for hospital admissions and urinary sepsis and are still associated with a 10 % risk of mortality [2–4]. This is also true for other at risk populations with neurogenic bladder, such as patients with myelomeningocele, for whom UTI is the most common diagnosis at admission, comprising 10 % of all hospital admissions [5].

In this chapter, our aim is to address the diagnostic and management considerations that arise with new and worsening infections in the reconstructed bladder, emphasizing evidence-based studies and common practices for these patients.

Definition of UTI

- Patients with neurogenic bladder may not be accurate in predicting when they have UTI and confirmatory cultures are useful.
- UTI should only be treated in patients with neurogenic or reconstructed bladders in the setting of symptoms (malaise, fever, increased spasticity, worsened autonomic dysreflexia, or cloudy and foul smelling urine).

Recurrent UTI in the general population, which can also be applied to patients with neurogenic and reconstructed bladders, is defined as three episodes of UTI in the last 12 months or two episodes in the last 6 months [6]. However, the definition of

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what constitutes a UTI in patients with neurogenic bladder who are utilizing clean intermittent catheterization (CIC) is controversial.

One definition of UTI in neurogenic bladder which has been proposed is bacteriuria >100,000 CFU/mL in combination with leukocyturia >100,000 CFU/mL. With asymptomatic leukocyturia of >100,000 CFU/mL, treatment is recommended only in the setting of a positive culture. Optimal mode of specimen collection is via catheterization, as samples obtained via spontaneous voiding can yield up to 2–4 different species due to contamination [7].

Patients with neurogenic bladder are not necessarily accurate in predicting the presence of UTI. In one study patients with SCI presenting to clinic with symptoms that they attribute to UTIs were only accurate 60 % of the time. This poor accuracy in predicting the presence of UTI did not depend upon the method of bladder management. In the patients who were not accurate, the symptoms experienced were later found to be attributed to medical problems that included other infectious causes, fecal impaction, bowel obstruction, dehydration, heat intolerance, glucosuria, respiratory problems, and neurologic problems [8]. The typical symptoms of UTI in patients with neurogenic bladder include fever, suprapubic or flank pain, urinary incontinence, increased somatomotor spasticity, autonomic dysreflexia, fatigue, turbid or malodorous urine, and restlessness [7]. Other presenting symptoms in patients with impaired sensorium can include headache, vague abdominal pain, and somnolence.

While the treatment of symptomatic UTI is routine, the issue of management of asymptomatic bacteriuria in a reconstructed urinary tract is less standardized, bringing up the question of when pyuria, bacteriuria, or malodorous urine should lead to diagnosis and treatment of a UTI [9]. Asymptomatic bacteriuria is often interpreted as silent colonization rather than infection. This approach is supported by the fact that there are frequently no accompanying acute phase reactants or a significant serum antibody response [10]. It is generally accepted that overtreatment of UTI has the potential of eliminating colonization that may be helpful in preventing infections with more pathogenic bacteria. However, the decision to abstain from treating asymptomatic bacteriuria is complicated by findings that even in the absence of symptoms, patients with neurogenic bladder can harbor biofilms. These aggregates of bacteria can lead to a significant (33 %) reduction in bladder cell viability, compromising the first line of defense against pathogens [11].

Routine urine specimens or cultures are not indicated and can lead to overtreatment, as >50 % of routine urine cultures in asymptomatic patients with neurogenic bladder have >100,000 CFU/mL of bacteriuria and half of these are multidrug resistant [12]. Despite this, in a survey of myelomeningocele clinics, 49 % perform routine urine cultures in addition to those triggered by the presentation of fever, frequency, dysuria, chills, abdominal pain, or urinalysis with >50 WBC/hpf [13].

Epidemiology and Incidence of UTI in Neurogenic Bladder

- CIC is associated with lower risk of UTI compared to indwelling catheters.
- Bacterial colonization is asymptomatic bacteriuria and is typically present in patients performing self-catheterization or with reconstructed bladders.

Overall, the annual incidence of UTI in SCI is 20 % [14]. The method of urinary drainage is an important factor in predicting the risk of UTI; the incidence of UTI in indwelling urinary catheter (IUC) is 2.7/100 person days, whereas for CIC, condom catheter, and normal voiding the incidence decreases to 0.41, 0.36, and 0.06/100 person days, respectively [2]. The incidence of bacteriuria is substantial, with a 70 % prevalence of bacteriuria of ≥100,000 CFU/mL in neurogenic bladder patients on CIC and 85–95 % in patients with IUC [15–18].

Chronic infections of the augmented bladder have been observed in 59 % of cases [19]. Rates are similar in incontinent ileovesicostomy, where 54–83 % patients experience infection [20]. In the clinical experience of our group with adult myelomeningocele patients (of whom the majority

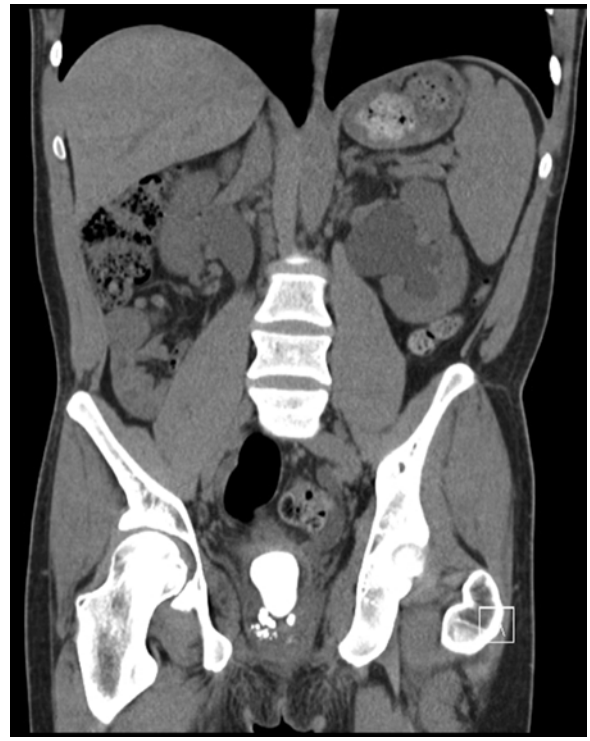

Fig. 9.1 Large bladder stones arising in a patient with neurogenic bladder and recurrent UTI

have had urologic surgery, most commonly a bladder augmentation), 34 % complain of symptomatic recurrent UTIs [21].

Workup for UTI in Patients with Previous Bladder Reconstruction

- Considerations in the workup of new or worsening UTI in patients with neurogenic or the reconstructed bladder should include:
  - Urolithiasis
  - VUR
  - Poor bladder compliance
  - Anatomic problems with previous surgery
  - Patient noncompliance with catheterization

Some of the common causes of new, recurrent, or worsening UTI in patients with a reconstructed bladder are stones arising from chronic stasis and bacteriuria, poor compliance and high pressures within the bladder, VUR, noncompliance with catheterization, inadequate bowel management, incontinence, and anatomic problems such as hydronephrosis or renal abscess. A workup for worsening urologic infection, in patients with neurogenic bladder and particularly reconstructed bladders, should accurately diagnose any of these problems that may be leading to symptomatic UTI.

Urolithiasis

- Rates of bladder stone formation are from 10 to 50 % in patients with augmentation cystoplasty.
- Daily irrigation is a mainstay to prevent recurrent stones from forming but can fail in up to a third of patients, who have formed stones in the past.

Following augmentation cystoplasty, the incidence of bladder stone formation is 10–52 % (Fig. 9.1) [22–24] with 15–25 % of all patients requiring a median of two cystolithalopaxy procedures [25, 26]. The postulated etiology of stone formation is mucus acting as a nidus in the presence of bacterial colonization and urinary stasis. Differing intestinal segments have variable risks of stone formation. For instance, though rarely utilized in contemporary treatments due to malignant potential and hematuria-dysuria syndrome,

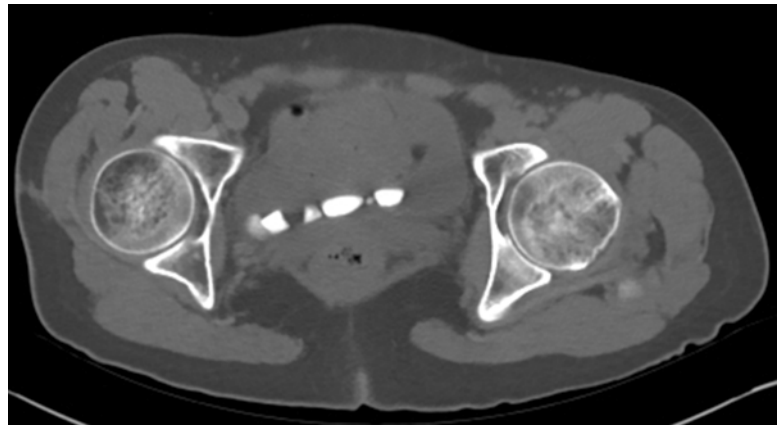

Fig. 9.2 Stones in the distal ureter that has been re-implanted across the trigone. This anatomy can make conventional retrograde approaches challenging or impossible

gastric segments are protective against stone formation [23, 27]. In contrast, the rates of stones in ileocystoplasty are 11–52 % [23, 24]. Other factors relating to bladder reconstruction may also contribute to stone risk in patients with enterocystoplasty. In a series of patients who had undergone enterocystoplasty, the risk of stone formation significantly increased when combined with a bladder neck procedure, catheterizable stoma creation, or both, corresponding to a 14.7 %, 14.3 %, and 21.1 % risk of stone formation, respectively [23].

The mean time to diagnosis of bladder stones following enterocystoplasty is approximately 5.5 years, and the most common presenting complaint is UTI [23, 25]. A urease-splitting organism was found in 89 % positive urine cultures and not unexpectedly, the proportion of struvite stones was the same [23]. A complete discussion of urolithiasis in congenital neuropathic patients, including management, can be found in Chap. 15 (Monga) in this textbook.

Following complete evacuation of the stone fragments, regular bladder irrigation can be employed to prevent stone recurrence. However, it is important to be aware that irrigation has been found to fail in 33–44 % of patients, who experience recurrence of stones [23]. Stone composition is most commonly carbonate apatite complexed with struvite, followed by ammonium acid urate [27]. All patients from the DeFoor stone series had chronically alkaline urine with a median urine pH of 7.5 and common bacterial pathogens identified on urine culture were *Proteus* and *Klebsiella* species. It is for this reason that suppression of UTI if possible may also be a very important part of decreasing stone formation in addition to bladder irrigation. Suppression of UTI may fall into a variety of categories, including finding strategies to rid a patient of chronic indwelling catheters, or treatment of abnormal bladder compliance.

Patients with neurogenic bladder are also at risk for upper tract stone formation. For instance, upper tract stones effect 30 % of tetraplegic patients regardless of history of prior urological surgery and is attributed to both immobilization and VUR of infected urine [28]. In the reconstructed bladder, typical retrograde treatment of upper tract stones may not be possible due to bladder neck procedures or a history of ureteral re-implantation and percutaneous nephrolithotomy must be performed in these cases (Fig. 9.2).

The workup for nephrolithiasis and/or bladder stones is variable. Renal ultrasound accompanied by a plain film of the kidneys, ureter, and bladder (KUB) will likely find most cases of large bladder and renal calculi. The most definitive test for urinary stones, however, is computed tomography (CT) scan, since uric acid stones may be radiolucent and missed in a KUB. A CT scan of the abdomen and pelvis can be done without contrast for patients with a dye allergy or renal insufficiency or it can be done with intravenous contrast (in order to obtain excretory phase images), which gives more information about the

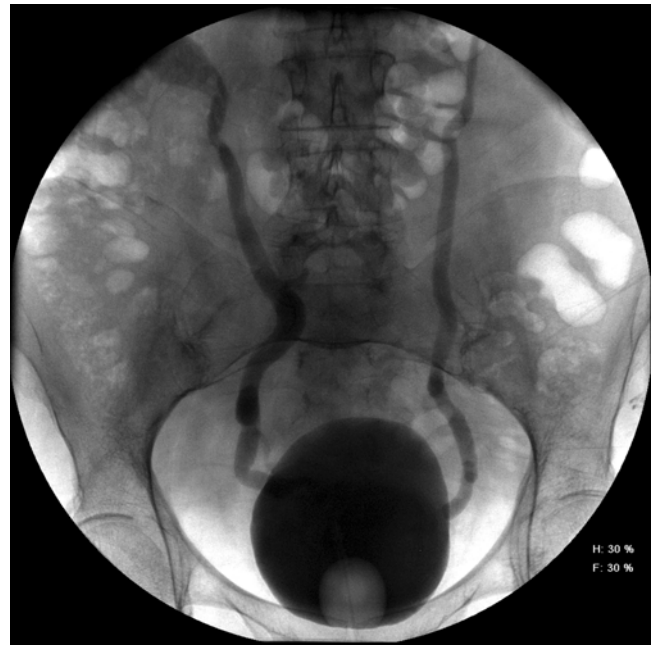

Fig. 9.3 Severe bilateral vesicoureteral reflux in a patient with poor compliance from neurogenic bladder

drainage of the kidneys and ureters, as well as identifying scars and evidence of ongoing pyelonephritis. A CT scan is indicated when new or worsening UTI is accompanied by hematuria.

Vesicoureteral Reflux

- VUR may lead to recurrent pyelonephritis episodes in patients with otherwise asymptomatic bacteriuria.
- There is contradictory evidence about the need to treat VUR at the time of augmentation cystoplasty.

The importance of VUR in adults is debatable. However, in patients with neurogenic bladder and reconstructed bladders it may be important to treat. New or worsening VUR can indicate worsening bladder compliance and a need for re-evaluation of pressures with a cystometrogram (urodynamics) (Fig. 9.3). VUR may complicate UTI because otherwise asymptomatic bacteriuria may ascend and cause febrile UTI and systemic symptoms. A large and dilated refluxing system may also act as a reservoir of static urine, where infection can arise. Some studies show that augmentation cystoplasty alone resolves or downgrades nearly all VUR in both adult and pediatric populations by restoring a low-pressure system [29–31]. These findings are controversial, however, and some recent studies have found opposite results. In one study of children undergoing augmentation cystoplasty with small bowel, low-grade VUR persisted in only 10 % of patients, however, high-grade VUR persisted in 47 %, and about half of these patients went on to experience pyelonephritis if they did not have treatment of VUR at the time of augmentation cystoplasty [32]. Conversely, patients who undergo ureteral re-implantation at the time of augmentation cytsoplasty were found to have complete resolution of high-grade VUR and a markedly decreased incidence of UTI [33]. Based upon these findings, authors recommended, ureteral re-implantation for high-grade VUR at the time of augmentation cystoplasty. Interpreting these contradictory results is difficult, however, and consideration should be given to the fact that treating VUR with ureteral re-implantation after augmentation is a much harder task than at the time of augmentation cystoplasty.

In follow-up regimens of patients with neurogenic bladder, it is often argued that patients should have annual or regular cystograms to

monitor for VUR. This recommendation may be unnecessary since there is very little data to support treatment of VUR in asymptomatic adults, other than for evidence of ascending infections that cause pyelonephritis episodes. A targeted approach in individuals who are having febrile UTI or evidence of pyelonephritis will save patients from many unnecessary cystograms and associated risks, such as induction of urosepsis or catheter trauma.

Poor Bladder Compliance and UTI Risk

- High-pressure bladder dynamics and poor compliance can be a major component of difficult to treat UTI
- Measures to improve bladder dynamics lessen UTI rates

Lapides popularized the concept that high intravesical pressure and bladder over distention is responsible for increased UTI risk. The postulated mechanism is that when the bladder is subjected to periods of reduced blood flow, its susceptibility to bacterial invasion is increased [34]. There is a substantial amount of indirect evidence supporting this theory. For instance, urodynamic testing in infants with UTI but without VUR showed high voiding detrusor pressures of 40–100 cm, suggesting that the high-pressure voiding itself, rather than an anatomic defect, predisposed these infants to UTI [35].

The link between high-pressure voiding and UTI is further illustrated by a decrease in the incidence of UTI through interventions that increase bladder capacity and decrease detrusor tone. For example, surgical release of spinal cord tethering has been found to increase bladder capacity and decrease detrusor leak point pressures, with a corresponding drop in febrile UTI [36]. Similarly, improved bladder capacity and decreased bladder pressures observed in patients with sacral nerve modulator implants, placed immediately after SCI, and has also been associated with a decreased incidence of UTI [37]. Other evidence supporting this concept is in patients with neurogenic detrusor overactivity due to multiple sclerosis (MS) or SCI who received detrusor injections of 300 U of onabotulinum toxinA. In this study, the number of UTIs over 6 months decreased from a mean of 1.75 to 0.2. Interestingly, those patients with persistent symptomatic urinary infections also demonstrated less improvement in their urodynamic parameters, reflecting the idea that improved reservoir capacity and lower pressures are protective against UTI [38]. In contrast to this study, however, it is important to note that UTI risk was higher in patients treated onabotulinum toxinA, in the DIGNITY trial. This increased risk was likely due to patients with MS starting intermittent catheterization. As part of the same study, the patients with SCI who were already performing catheterization did not have a decrease in UTI, but UTI was only defined as positive cultures, which were routinely obtained during follow-up and there was no quantification of symptomatic UTI.

When compliance is felt to be a major issue, then a urodynamic study (cystometrogram) is warranted. Even in patients with previous bladder augmentation a low capacity and poor compliance bladder may be an issue. In fact, up to 9 % of patients with a history of pediatric augmentation cystoplasty require re-augmentation [25, 26, 39]. A bladder journal documenting the patient's functional volumes can also provide vital information about their capacity and identify patients who might benefit from urodynamics.

Anatomic Problems

- Anatomic problems that need surgical correction are commonplace in patients with reconstructed bladders.
- Increased UTI rates can be caused by problems such as ureteropelvic junction obstruction or stenosis of the distal ureter at the site of previous ureteral re-implantation.

Among patients who have undergone bladder reconstruction, in particular augmentation cystoplasty, 34–40 % can be expected to require an additional urological procedure in the future. The most common surgery is cystolithalopaxy,

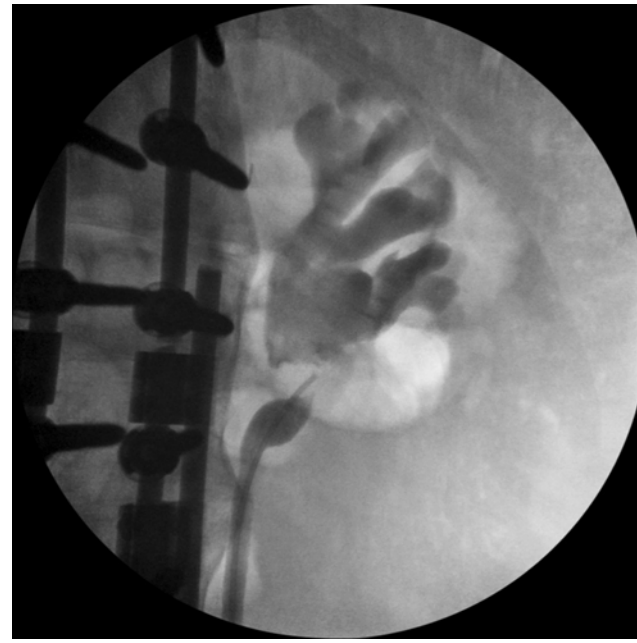

Fig. 9.4 Ureteropelvic junction obstruction in a patient with spinal cord injury that may have arisen from congenital issues, scarring, or ureteral redundancy

accounting for 25 % of interventions post-augmentation, with a median of two occurrences of stones [25, 26]. In regard to major revision surgery, urinary diversion is required in 5 %, repair of bladder rupture in 3 %, treatment of small bowel obstruction in 3 %, and re-augmentation in 9 % due to issues with persistent incontinence, isolated upper tract changes, and detrusor pressure of >30 cmH_2O [25, 26, 39]. Revision rates for a catheterizable channel have also been reported to be as high as 20 % [40], and in our experience up to 50 % of patients require revision surgery for tunneled catheterizable channels [21]. While many of these operative problems do not lead to increasing UTI, they serve to emphasize that anatomic problems which need to be addressed with surgery are commonplace after bladder reconstruction.

When UTI begin or worsen in patients with previous bladder reconstruction or augmentation, it is important to fully evaluate any anatomic reasons that could be contributing. One of the most important considerations is kidney obstruction from previous ureteral surgery. While ureteral re-implant surgery to treat VUR has a very low stenosis rate long term, this may not be true in neurogenic bladder patients. The neurogenic bladder is fundamentally quite different; it is thickened and fibrotic, lacking normal elasticity and may have been adversely affected by years of chronic cystitis. All of these factors can lead to recurrent VUR or stenosis. As mentioned above, VUR can be a cause of febrile UTI in patients due to pyelonephritis and is evaluated with a cystogram. Ureteral stenosis is evaluated with a nuclear medicine lasix renogram. It is often difficult to interpret the results of lasix renograms, however, given that many patients who have had chronic hydronephrosis may exhibit some degree of delayed emptying. In cases that are equivocal, we often perform retrograde or antegrade ureteral pyelography.

Another anatomic problem that we have seen arise in patients with neurogenic bladder and previous bladder reconstruction is ureteropelvic junction obstruction (UPJO). There is a small incidence of UPJO associated with VUR that has been established in pediatric urology. These cases of UPJO may be due to this association, or they may arise secondary to fibrosis surrounding the ureter from ascending infection, stones, or previous manipulation (Fig. 9.4). Other causes are redundancy arising from chronic hydronephrosis secondary to a history of VUR and high-pressure bladder dynamics. Ureteral redundancy can cause a kinking effect in the ureter and in

some cases can lead to a functional obstruction. An evaluation can be performed with a nuclear medicine lasix renogram, potentially in combination with retrograde ureteropyelograms [41].

Finally, the shape of the reconstructed bladder itself can be a predisposing factor for recurrent infections, as when the bladder enlarges and gains a saccular shape. This can create a situation in which portions of the bladder are not drained to completion with intermittent catheterization, resulting in urinary stasis. Such a situation can be diagnosed using cystogram before and after catheterization, and may be a diagnosis of exclusion after all other sources of urinary infections has been ruled out. One approach to managing an incompletely draining reconstructed bladder is scheduled manual irrigations through a catheter followed by active aspiration of the irrigant.

Clean Intermittent Catheterization

- Noncompliance with catheterization schedules can increase UTI rates.
- There is contradictory evidence to suggest hydrophilic catheters offer any advantage.

A regular schedule of CIC has been shown to be safe and effective in the long term and can avoid bladder distention and high intraluminal pressures, allowing bacteria introduced by CIC to be neutralized. The rate of UTI and bacteriuria, as well as other urologic complications are lower in patients who use CIC compared to indwelling catheters, and thus is the recommended option [42].

In a bladder with normal capacity and compliance, the frequency of catheterization is every 4–6 h, with an aim to maintain bladder volumes <500 mL. However, given the varied bladder compliance and capacity in patients with neurogenic or augmented bladders, the regimen must be individualized on a case-by-case basis. Typically 12–16F catheters are used for both adult men and women, with larger catheters employed in augmented bladders requiring irrigation. Clean, as opposed to sterile, intermittent catheterization does not pose an increased risk of symptomatic UTI in SCI patients and has significant cost and time saving benefits [43]. When it comes to catheter selection, there is contradictory evidence about the use of hydrophilic catheters, with some studies showing lower rates of infection and hematuria compared to non-hydrophilic catheters [44].

Of adult patients who have been instructed on CIC, only about 2/3 are compliant with at least 80 % of the initial recommendation at 1 year [45]. Noncompliance with catheterization leads to overflow incontinence, which in itself can contribute to UTI risk [46, 47] as well as higher rates of UTI due to more time spent with elevated intravesical pressure. A very simple way of assessing catheterization volumes, leakage, and patient compliance is to have patients keep a bladder journal for several days.

Prevention Strategies for UTI

Once modifiable problems with the urinary tract have been eliminated or treated and UTI remains as a persistent issue, then treatment should focus on prevention of infections. Prevention strategies are best employed in a very systematic and stepwise fashion starting with therapies that minimize chronic antibiotic use. Some of these strategies are in development such as bacterial interference, while others are commonly used. The evidence underlying these strategies is often contradictory or lacking; however, they are often tried in an effort to control UTI in patients who are commonly very affected by their UTI.

Bladder Irrigations

- Bladder irrigations with NS or water are safe and effective in evacuating bacteria, associated biofilms, and mucous.
- Irrigation with antibiotic solutions can also be used; however, their superiority to NS or water irrigations has not been established.

The use of gentamicin bladder irrigation in augmented bladders is common [48] and has been demonstrated to be safe with little systemic absorption [49]. When compared to a control group of no treatment, both neomycin/polymyxin B and

kanamycin/colistin irrigations have demonstrated efficacy in reducing incidence of bacteriuria in SCI patients with neurogenic bladder [50, 51]. However, when neomycin-polymyxin irrigations were compared to irrigations with sterile saline or acetic acid, there were no differences in bacteriuria or pyuria [52]. Additionally, bladder irrigation with sterile NaCl 0.9 % versus tap water has shown no difference in the incidence of positive urine cultures [53]. This observation lends support to the theory that the mechanical effect of a washout rather than the antiseptic properties of the agent being instilled is what ultimately helps in controlling the bacterial burden in patients.

Acidic bladder washout solutions have been shown to be superior to saline in reducing struvite crystals, however whether this decreases stone formation is unclear [54]. Approaches to stone prevention proposed by DeFoor et al. include an early regimen of regular low-volume bladder irrigation, with a transition to high-volume bladder irrigation regimen after stone development and treatment. In the event of recurrent stone formation on high-volume irrigation, 20 % urea solution irrigation is proposed, although it is yet to be proven effective [27]. Compliance is the main barrier to the efficacy of irrigations in UTI prevention. A 4-year study of children with ileocystoplasty demonstrated with close monitoring of compliance with an irrigation regimen, UTI can be virtually eliminated and stone incidence can be decreased to 7 % [55].

Bowel Management

The link between functional constipation and recurrent UTIs has been well documented, especially in the pediatric population. A recent study of children with myelomeningocele found a correlation between the intestinal production of methane, prolonged orocecal transit time, and a higher incidence of UTIs [56]. In another study of pediatric patients with lower urinary tract dysfunction, almost half of patients with constipation also experienced UTIs [57]. One proposed mechanism is that the distended rectum in a constipated child produces obstruction of the bladder outflow. Another hypothesis is that intestinal stasis causes overgrowth of bacteria, which then translocates to the genitourinary tract. Approaches to improved bowel management include an oral regiment of laxatives, colonic stimulants, and stool softeners, retrograde enemas, or antegrade enemas via a continent appendiceal stoma. In the adult population of patients with neurogenic bowel, digital stimulation, manual disimpaction, and suppositories are additional approaches to attain regularity and minimize direct contamination of the urethra that can be the result of encopresis.

Prophylactic Antibiotic Regimens

- Prophylactic antibiotics may decrease UTI rates with the significant downside of higher rates of resistant infection.

In SCI patients, the use of long-term systemic antibiotic prophylaxis achieves only modest protection against UTI, at the expense of an increase in antimicrobial resistance and adverse drug reactions [58, 59].

However, prophylactic antibiotic treatment needs to be considered in patients with recurrent UTIs, high-pressure bladders, and a dilated upper urinary tract which predispose patients to urosepsis. Some authors recommend a 3-month course of prophylactic antibiotics if UTIs persists after treatment of an established infection [60].

Commonly utilized prophylactic antibiotic agents include oral trimethoprim and sulfamethoxazole, nitrofurantoin, and ciprofloxacin. Often these are used at one half to a quarter of a daily dose for 6 months. In pediatric patients on CIC for neurogenic bladder, a 10 % decrease in bacteriuria and a 50 % decrease in symptomatic UTIs were observed on nitrofurantoin prophylaxis compared to placebo. Bacterial species responsible for bacteriuria were altered in the nitrofurantoin group, with *E. coli* being replaced by resistant *Klebsiella* and *Pseudomonas* species with a tripled rate of resistance [61]. In contrast, antimicrobial prophylaxis in adult patients on CIC did not affect the incidence of symptomatic UTI compared to placebo [62]. A meta-analysis of adult patients with SCI revealed that antimicrobial prophylaxis did not significantly decrease

symptomatic infections. Prophylaxis was associated with a reduction in asymptomatic bacteriuria among acute patients (<90 days after SCI), with the finding that one patient would require 3.7 weeks of treatment on average to prevent one asymptomatic infection. Prophylaxis resulted in an approximately twofold increase in the proportion of antimicrobial resistant bacteria [58].

Cyclic High-Dose Antibiotics for UTI Prophylaxis

- Another antibiotic-based suppressive regimen is keeping patients on weekly cyclic high-dose antibiotics.

An observational prospective study evaluating the efficacy of alternating once-weekly oral cyclic antibiotic (WOCA) regimen over 2 years to prevent UTI in SCI adult patients with neurogenic bladder undergoing CIC, revealed a significant decrease in the incidence of UTI. Before intervention, there were 9.4 symptomatic UTIs per patient-year, including 197 episodes of febrile UTI responsible for 45 hospitalizations. Under the WOCA regimen there were 1.8 symptomatic UTI per patient-year, including 19 episodes of febrile UTI. No severe adverse events and no new cases of colonization with MDR bacteria were reported [59]. In our anecdotal experience, the WOCA regimen appears to be quite helpful for some patients that struggle with recurrent symptomatic UTI and we often offer this over daily low-dose prophylaxis. Complications and limitations to this strategy are the development of *Clostridium difficile* colitis and baseline-resistant UTI.

Cranberry

- Although cranberry extract is commonly used to suppress UTI, the evidence is contradictory and a recent Cochrane review found little evidence to support its use.

The postulated mechanism of action of cranberry is the effect of a proanthocyanidin molecule contained within cranberries that impairs bacterial adherence to the urothelium, thereby reducing the biofilm load of both Gram-negative and Gram-positive bacteria [63]. In a randomized placebo-controlled study with crossover design of SCI patients with neurogenic bladder, cranberry extract administration reduced the frequency of UTI to 0.3 per year, compared to 1 UTI per year on placebo. Subjects with a glomerular filtration rate (GFR) greater than 75 mL/min received the most benefit [64]. In contrast, a 1-year study comparing cranberry extract (36 mg proanthocyanidins BID) versus placebo in adult MS patients with urinary disorders demonstrated no difference in incidence of UTI [65]. Similarly, a cross-over study of patients with neurogenic bladders due to SCI and requiring catheterization randomized to 400-mg cranberry tablets TID for 4 weeks or placebo demonstrated no difference in urinary pH, bacteriuria, or pyuria [66]. In the 2013 Cochrane review, cranberry products were not found to significantly reduce the risk of repeat symptomatic UTI compared to placebo for any subgroups, including women with recurrent UTIs and patients with neurogenic bladder or SCI [67].

D-Mannose

- D-Mannose in randomized studies of limited populations is as effective as daily antibiotics in suppressing UTI rates.

D-Mannose is a naturally occurring sugar used by the human metabolism in protein glycosylation. It has been shown to bind to and block FimH adhesin on the fimbria of enteric bacteria as well as bind to urothelial glycoprotein receptors, thereby inhibiting bacterial adherence. When used for a 6-month interval in women with recurrent UTI, the incidence of UTI in the D-MANNOSE and nitrofurantoin groups was 15 % and 20 %, respectively, compared to 60 % in the group receiving no prophylaxis [68]. D-mannose has yet to be evaluated in neurogenic and augmented bladders.

Methenamine and Vitamin C

- Methenamine salts are metabolized to formaldehyde in acidic urine.
- Evidence is contradictory for the use of methenamine, with some studies showing benefits in preventing UTI and others showing no benefit.

Methenamine salts (mandelate and hippurate) are antiseptics that undergo conversion to formaldehyde in urine. The favorable characteristics of methenamine include the absence of bacterial resistance to formaldehyde, lack of effect on bowel flora, and low cost [58, 69]. When administered with ammonium chloride for acidification, methenamine has been shown to significantly reduce the incidence of UTI in patients with neurogenic bladders [70]. The combination of oral methenamine with bladder instillations of hemi-acridin for acidification has been shown to reduce the incidence of bacteriuria in patients undergoing intermittent catheterization [69]. Reviews of trials of methenamine hippurate used in various populations confirmed its efficacy in reducing the number of symptomatic UTI and bacteriuria in patients without renal tract abnormalities, but not in patients with known renal tract abnormalities, neurogenic bladder, or indwelling catheters [71, 72].

Trisdine

- In very limited trials, installation of Trisdine (chlorhexidine gluconate) decreased UTI rates in patients doing CIC.

Intravesical instillations of Trisdine, an aqueous solution of chlorhexidine gluconate, have been shown to significantly lower incidence of bacteriuria compared catheterization alone in patients with SCI utilizing CIC [73]. This single study has not been replicated. However, it is feasible that with future research, installation of some antiseptic agent that is not caustic to the bladder urothelium might prove to be a beneficial strategy.

Bacterial Interference

- Bacterial interference is intentional colonization with minimally pathogenic forms of *E. coli*.
- While promising, this strategy has yet to be borne out in large studies.

Bacterial interference has been recently studied for UTI prevention. Treatment entails the deliberate intravesical introduction of nonpathologic bacteria in order to prevent infection with more virulent bacteria. The concept emerged from observations that untreated asymptomatic bacteriuria prevents symptomatic UTI [74, 75]. A strain of *Escherichia coli* (strain 83972) was isolated from a woman with spina bifida who demonstrated persistent colonization, but never manifested with a clinical UTI. This strain of bacteria has been used to intentionally colonize the bladder of patients at risk for recurrent symptomatic UTI, in a process that has been referred to as bacterial interference. The genome of *Escherichia coli* strain 83972 lacks expressed virulence factors such as P-fimbriae as well as a defined O:K:H serotype 12 and is sensitive to all common antibiotics for UTI. In addition, it carries a small plasmid enabling identification [76].

Following inoculation, persistence of colonization has been documented at a mean of 12.3 months (range 2–40) in SCI patients with neurogenic bladder and a history of recurrent UTIs. Colonization was not associated with fever, or other symptoms of genitourinary or systemic illness. Bacteriuria was associated with pyuria and persisted for as long as bacteriuria remained. The bacteria elicits a local immune response, but of insufficient magnitude to produce symptoms. Hull et al. demonstrated that of the subjects who were successfully colonized, none developed symptomatic UTIs over the 18 patient-years studied as compared to mean of 3.1 UTIs per year (range 2–7) prior to colonization [9]. Another study utilizing similar methods did observe UTIs in the colonized group; however, efficacy was demonstrated as delay to the first UTI (median

11.3 with colonization vs. 5.7 months without) and about 60 % fewer reported UTI episodes with vs. without *E. coli* 83972 bacteriuria [76]. Other strains of non-pathogenic *E. coli* with even less potential for virulence are under development [77]. The limitations of bacterial interference include failure to colonize after multiple inoculation cycles, elimination of colonization following antibiotic treatment for non-genitourinary infections, and spontaneous loss of colonization [9]. Although this may be a promising future therapy, bacterial interference needs to tried on a larger scale and there are currently no commercial products that are available using this strategy.

Conclusions

UTIs in patients with congenital neurogenic and augmented bladders that result in significant patient morbidity are multifactorial and difficult to manage. Bacteriuria is ubiquitous in patients with neurogenic bladder, and in general, it should not be treated, unless the patient is symptomatic or is planning to undergo an invasive urological procedure. Some of the causes of new or worsening UTI in patients with neurogenic or reconstructed bladder include stone formation, high-pressure bladder dynamics, VUR, anatomic problems with previous surgery, and noncompliance with catheterization.

Treatment strategies for UTI prevention include increased frequency of bladder irrigation, improved bowel management routine, suppressive low-dose daily antibiotics, high-dose weekly oral cyclic antibiotics, the use of supplements of cranberry and/or D-mannose, antibiotics installation and washout of the bladder, and possible the instillation of direct antiseptics with catheterization. Generally, evidence is not strong for any of these therapies; however, they may work on individual patients. Other promising therapies involve bacterial interference strategies with intentional colonization of the bladder with non-pathogenic bacteria. Due to the complexity and high risks associated with UTIs in the population of patients with neurogenic and augmented bladders, close urological monitoring is crucial to early diagnosis and timely management.

Summary

- Symptoms of UTI in patients with neurogenic bladder may be nonspecific and confirmatory cultures are useful.
- Bacterial colonization is asymptomatic bacteriuria and is typically present in patients performing self-catheterization or those with reconstructed bladders. Therefore, UTIs should only be treated in this population if they are symptomatic.
- CIC is associated with lower risk of UTI compared to indwelling catheters.
- Factors that can lead to new or worsening UTI in patients with neurogenic or reconstructed bladder can include urolithiasis, VUR, poor bladder compliance, anatomic problems leading to compromised drainage of the ureters or bladder, and noncompliance with catheterization.
- Preventative strategies for recurrent UTIs in neurogenic or reconstructed bladder include irrigation (NS, water, or antibiotics), CIC, optimization of bowel function, prophylactic antibiotics, D-mannose, cranberry, and bacterial interference.

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Troubleshooting Continent Catheterizable Channels

10

Balaji Kalyanaraman and Sean P. Elliott

Introduction

Cutaneous continent catheterizable channels are effective in facilitating bladder emptying while maintaining body image, cosmetic appearance, and urinary continence [1]. Furthermore, they allow intermittent catheterization for wheelchair-bound patients who might otherwise not be able to catheterize per urethra. Lastly, patients with limited dexterity due to quadriplegia find it easier to catheterize through an abdominal stoma than the native urethra. The components of a continent catheterizable channel are cutaneous stoma, catheterizable conduit from the skin to reservoir, continence mechanism, and reservoir (native or augmented bladder).

Continence is achieved by one of the three mechanisms: (1) flap valve, (2) nipple valve, or (3) hydraulic valve. An example of the hydraulic valve was described by Benchekroun et al. [2]; however, acceptance has been low and this technique will not be discussed further. Paul Mitrofanoff popularized the flap valve technique when he described the creation of a continent appendicovesicostomy by tunneling the appendix submucosally into the bladder and maturing the stoma to the umbilicus [3]. The Mitrofanoff flap valve principle has been modified to fashion continent channels from tissues such as detubularized ileum (Yang-Monti, Casale), colon, ureter, and fallopian tube [4, 5]. Ileal channel cecocystoplasty (ICCC) uses detubularized cecum for bladder augmentation and tapered terminal ileum as the catheterizable channel; the ileocecal valve (Bauhin's valve) is reinforced and serves as a nipple valve for continence [6]. Another well-known example of a nipple valve is the Kock pouch, which uses an intussuscepted ileocecal valve and can be modified for an efferent limb from the native bladder [7].

Complications of continent channels can arise from any of the above mentioned components and include stomal stenosis, conduit stricture, diverticulae, false passage, and stomal incontinence. Patients can either present with difficulty/inability to catheterize (obstruction), leakage of urine from the channel (incontinence), or a combination of the two. Accurate diagnosis and appropriate management is paramount because for many of these patients, clean intermittent catheterization is the only way to empty the bladder. This chapter provides a framework to troubleshoot common complications of continent catheterizable channels.

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Obstruction

Patients with stomal stenosis, channel stricture, or false passage most often present with difficulty or inability to catheterize the channel. Some patients may complain of bleeding at the stoma as a result of traumatic catheterization.

Stomal stenosis is the most commonly reported complication in the literature, with rates ranging from 6 to 39 % for tunneled channels [8]. Most often, the stoma is located at the umbilicus for cosmetic reasons. In some patients, the stoma may be located in the right or left lower quadrant. Typically, a lower quadrant stoma is created if the conduit is made out of ureter so that the conduit can take a direct path from the retroperitoneum to the skin. A lower quadrant stoma may be chosen for an appendiceal Mitrofanoff if the mesentery is too short to reach the umbilicus without tension [9]. Thus far, no study has conclusively established the choice of stoma site as a factor in stomal stenosis. Other than cutaneous continent vesicostomy (CCV), the choice of tissue type for conduit creation does not seem to affect stenosis rates. CCV is associated with higher complication rates including stomal stenosis and channel fibrosis, thereby making it an option to be used only as a last resort [8, 10].

Stomal stenosis occurs relatively early in the postoperative course. Studies that have investigated the timing of channel complications suggest most cases of stomal stenosis occur in the first 20 months after surgery, with a mean duration to stenosis ranging from 7.75 to 13 months [8, 11, 12]. However, patients are known to present with stomal stenosis even as late as 5–6 years after initial surgery [12]. Ischemia at the mucocutaneous junction is hypothesized to be the most likely cause of stomal stenosis [8, 11]. Therefore, at the time of initial surgery, it is important to avoid tension on the channel and to preserve its blood supply as much as possible. In an effort to reduce the incidence of stenosis, the stomal end of the channel is frequently spatulated and a broad-based local skin flap in the shape of a "V" is advanced into the spatulation. Khoury et al. have described a technique which involves excising the umbilical scar and eversion–inversion of the umbilicus during stoma maturation [13]. The stenosis rate with this technique was found to be 8 %. Landau et al. have described a "V-quadrilateral-Z" skin flap for stoma maturation and early results in small number of patients showed no occurrence of stenosis [14].

Channel stricture occurs at a rate of 4–20 % in tunneled channels and its timing is similar to that of stomal stenosis [8, 11]. Ischemia plays a role in the development of channel stricture. False passage in the channel can result from traumatic catheterization in the presence of a stricture or due to incorrect catheterization technique [11]. Narayanaswamy et al. have reported a high rate of diverticular pouch formation in double Monti channels [15]. It is recommended to create channels with short extravesical segments in order to prevent subfascial complications such as false passage and diverticulum formation [16].

Incontinence

Incontinence from the stoma can be attributable to the continence mechanism, the reservoir, or both. The reported rates of channel incontinence range from 1 to 22 % and the timing can be variable [8]. However, the definition of stomal incontinence is not consistent among studies.

The continence mechanism in tunneled channels is dependent on creation of an adequate detrusor or submucosal tunnel (Mitrofanoff principle). In ICCC, the continence mechanism is the native ileocecal valve, which can be augmented by plication of the terminal ileum. Early channel incontinence related to the continence mechanism is more likely to be due to technical error, whereas late-onset incontinence might represent dilation of the tunnel with time [8]. Incontinence due to failure of the continence mechanism is typically large volume. On the other hand, incontinence due to the reservoir is typically small volume and can result from primary detrusor overactivity (DO) or secondary causes such as urinary tract infection (UTI) or bladder calculi.

Management of Catheterizable Channel Complications

Some of the principles of troubleshooting complications related to catheterizable channels would be familiar to most adult general urologists. Figures 10.1 and 10.2 provide a framework for stepwise management of the most commonly encountered complications.

Obstruction

Inability to catheterize the channel requires emergent intervention in patients whose bladder neck has been surgically closed or narrowed. In patients with a patent urethra and bladder neck, the situation is less dire. The patient, caregiver or healthcare provider can initiate intermittent urethral catheterization or place an indwelling urethral catheter until the channel obstruction can be addressed. Still, channel access should be re-established within a couple of days; it has been our experience that earlier intervention is more successful than delayed intervention.

The first step in obtaining channel access is a gentle attempt at catheterization using a well-lubricated catheter of the same or lesser size as routinely used by the patient. If the urethra is patent, a urethral catheter should be placed before attempting to catheterize the channel because a distended bladder can complicate catheterization of the channel in a couple of ways: (1) the channel can become kinked as the bladder distends and moves closer to the stoma; (2) the distended bladder will tighten the Mitrofanoff tunnel. If an initial attempt at channel catheterization is unsuccessful, then a second attempt with a hydrophilic guidewire can be helpful. However, before causing too much trauma, the urologist should have a low threshold to perform endoscopy of the channel and place a catheter over a wire. The small diameter of the catheterizable channels usually means that endoscopy should be done with a flexible pediatric cystoscope, flexible hysteroscope, or a flexible adult ureteroscope. A rigid pediatric cystoscope can be better suited for cases of stomal stenosis. When the urethra is patent, endoscopic attempts can be combined with transurethral cystoscopic guidance.

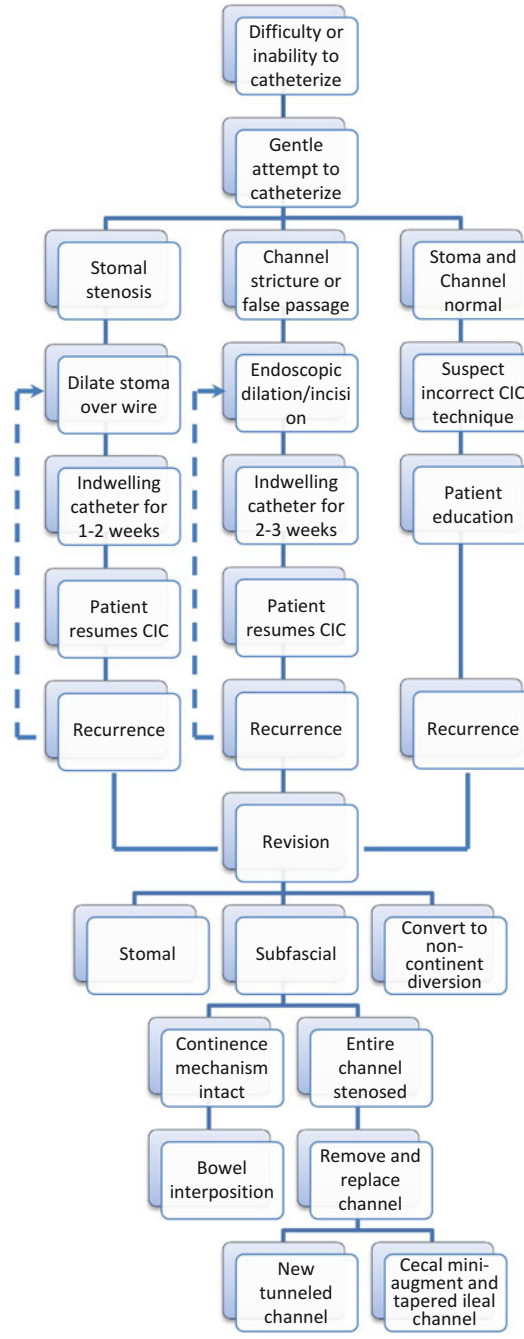

Fig. 10.1 Stepwise approach to troubleshoot obstruction in catheterizable channels

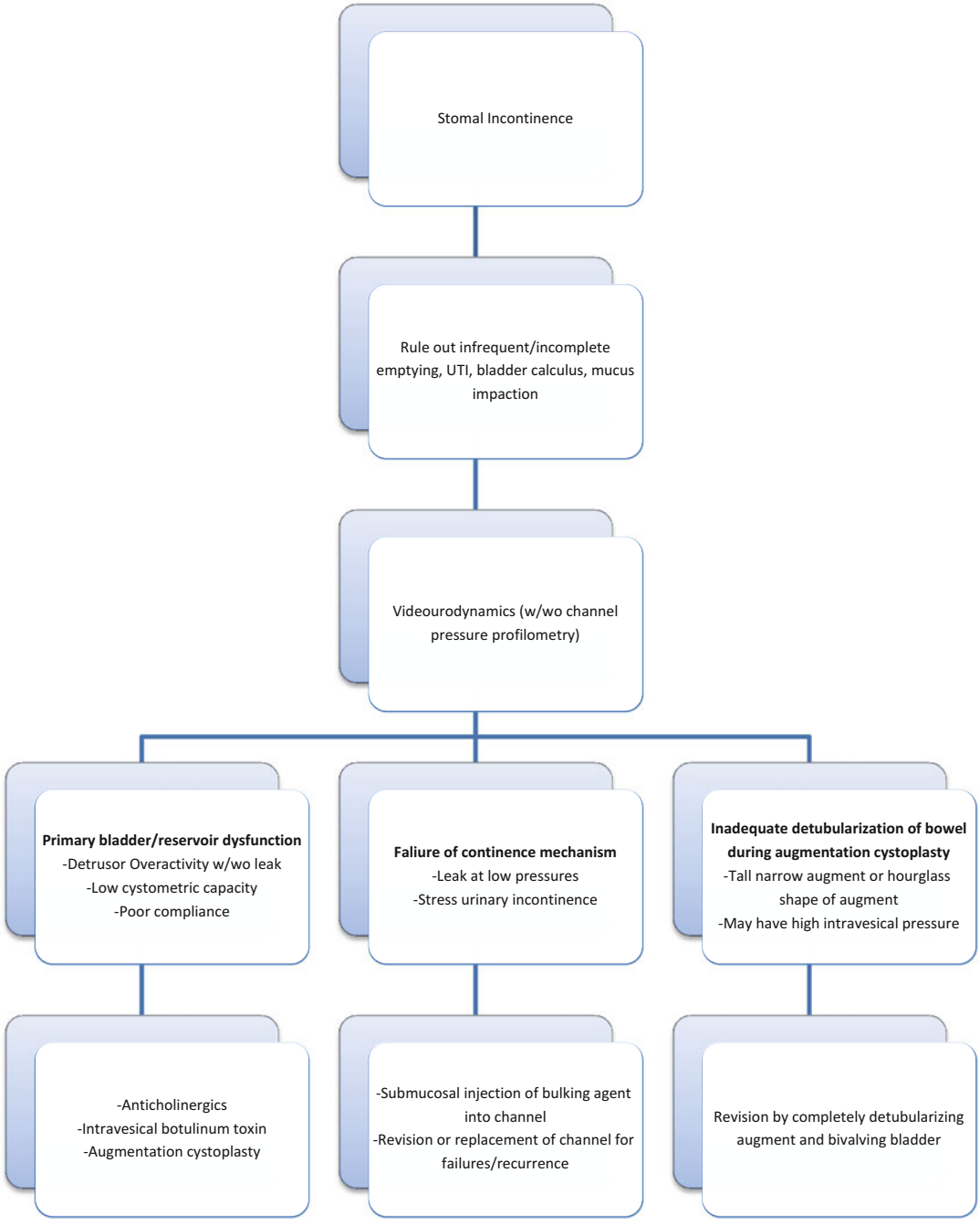

Fig. 10.2 Stepwise approach to troubleshoot incontinence through catheterizable channel

Dilation of the stoma or channel can be performed over the wire. We prefer to do this with a series of successively larger straight catheters over the wire. Dilation should not exceed the normal size of the channel—excessive dilation risks injury to the rest of the channel and the continence mechanism. Welk et al. have reported the use of steroid lubricant after stomal dilation to keep the stoma patent, although the durability of this treatment is not known [8]. Endoscopic incision of

channel stricture has been described although we prefer dilation to incision because of the fragile nature of catheterizable channels and the risk of injury to adjacent bowel. Once a catheter is placed, it should be left in place for 1 or 2 weeks following which the catheter can be removed and patient asked to resume CIC.

If initial endoscopic attempts fail and bladder drainage cannot be obtained through urethral catheterization, then suprapubic tube (SPT) placement should be considered. Although percutaneous SPT placement can be performed faster and with local anesthesia, the reconstructed lower urinary tract in many of these patients may necessitate open cystotomy and SPT placement. If the surgeon is facile with ultrasound-guided SPT placement, then this is a less invasive alternative to safely placing an SPT when adjacent bowel is of concern. Definitive management can then be planned on an elective basis, keeping in mind that the solution can be as simple as stomal revision or require removal and replacement of the channel. Mickelson et al., have described an "L-stent" which can be used for refractory stomal stenosis. This can act as a temporizing measure until surgical revision, or in some cases, obviate the need for surgery altogether [17].

Definitive management is indicated if endoscopic attempts fail or if obstruction recurs despite minimally invasive interventions. Stomal stenosis can be corrected by excising the scarred tip and advancing a local skin flap into a spatulated, healthy distal segment, as a Y-V plasty. We perform this with a wire in the channel when possible and dissect circumferentially down to fascia in order to mobilize a healthy segment of channel. This is a relatively minor procedure that can be accomplished in the ambulatory setting. Buccal mucosa graft can also be used for stomal revision as described by Radojicic et al. [18]. If the channel stricture is below the level of fascia, laparotomy is required for revision; unfortunately, this can be hard to predict preoperatively so we prepare all patients for the possibility of a laparotomy.

Upon laparotomy, identification of the stenosed portion of the channel is usually straightforward—even the outer wall of the channel is ischemic and fibrotic. Depending on the length of the involved segment, the channel can be revised by interposition of a segment of bowel or the entire channel may need to be removed and replaced (see Fig. 10.1). If only the distal portion of the channel is fibrosed and the continence mechanism is unaffected, then a new channel can be fashioned (e.g., Monti) and anastomosed end-to-end to the healthy end of the existing channel. If the entire channel is fibrotic, it should be resected and a new channel created. Ideally, the new channel is tunneled in the native bladder. However, if bladder size or chronic cystitis and mucosal inflammation preclude formation of a good detrusor tunnel, then a channel using an alternative continence mechanism must be entertained. A rather simple salvage procedure in this case is to add an ICCC to the native bladder or augment, using the ileocecal nipple valve for continence. A more challenging alternative that we reserve for cases in which the ileocecal valve is not available is the intussuscepted ileal flap valve [19].

Incontinence

In a patient with stomal incontinence, it is important to rule out causes such as infrequent catheterization, incomplete bladder emptying, UTI, bladder calculus, or mucus impaction. In the absence of such causes, urodynamic studies (UDS) can help determine the etiology of incontinence. Pressure profilometry of the channel can be performed at the time of UDS; however, there is no standard cut-off below which the value might be considered abnormal. If urethral access is present, the UDS catheter can be placed transurethrally and patient filled and stressed to demonstrate leakage with stress or with bladder filling to a specific volume. Low-pressure leakage, stress urinary incontinence, and the absence of detrusor overactivity (DO) would implicate the continence mechanism as the cause of incontinence. On the other hand, the presence of DO, leak with DO, or impaired compliance implies primary bladder pathology. Treatment can then be directed toward rectifying the cause of the incontinence (Fig. 10.2). If detrusor overactivity is

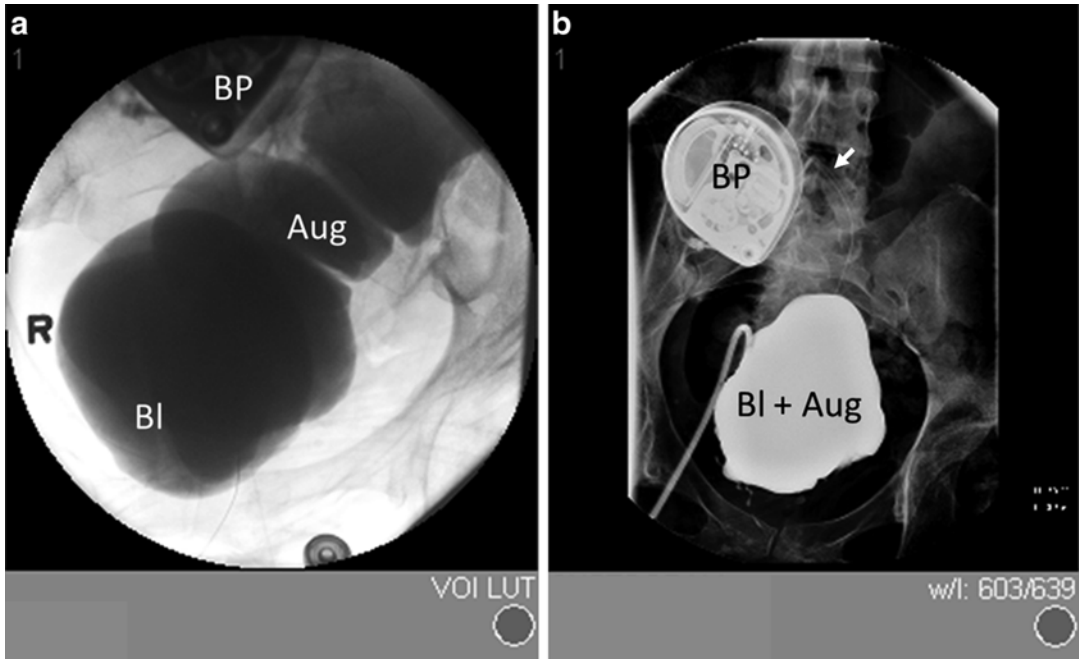

Fig. 10.3 (**a**) Cystogram of a patient with stomal incontinence showing an inadequately detubularized augment (Aug). The native bladder (Bl) is seen in the foreground, and there is a narrow communication between the bladder and augment. (**b**) Postoperative cystogram of the same patient after revision surgery by detubularizing the augment and anastomosing to a widely bivalved bladder. There is no transition between the native bladder and augment. *Arrow* points to the catheter in the continent channel. *BP* Baclofen pump

identified as the cause of incontinence, conservative measures such as anticholinergic medications and intravesical Botulinum toxin-A should be tried first. If the patient does not respond to such measures, he/she may be a candidate for augmentation cystoplasty or revision of an existing augmentation cystoplasty.

Endoscopic injection of bulking agents into the channel can be an effective, minimally invasive method to address failure of continence mechanism. Biomaterials that have been used for this purpose include collagen, PDMS, and dextranomer/hyaluronic acid injection (Deflux®). Prieto et al. have reported success rate of 71 % after a single injection and 79 % after two injections of Deflux in patients who were candidates for surgical revision for stomal incontinence. The mean follow-up duration in this series was 1 year [20]. Longer term studies are necessary to assess the durability of response with bulking agents. If incontinence does not respond to bulking agents, surgical intervention may be necessary. Revision of the existing continence mechanism, or removal and replacement of the entire channel with tunneled detubularized ileum (Monti), ICCC, or intussuscepted ileal flap valve as discussed in the earlier section can be considered. Yachia and Erlich have described the technique of creating a continent stoma by cross-wrapping non-detached strands of rectus muscle around the efferent channel. In their series of 17 patients, 100 % continence was reported after a mean follow-up duration of 32 months. Although described for primary creation of a continent reservoir, this technique can also be used as a salvage maneuver in cases of failure of continence mechanism [21].

In patients who have undergone augmentation cystoplasty, we have encountered instances wherein the incontinence is related to inadequate detubularization of bowel and/or bivalving of the bladder at the time of initial surgery. In such patients, cystogram reveals an "hourglass" configuration of the augmented bladder (Fig. 10.3). Revision of the augment by performing complete

detubularization of the bowel segment and maximal anteroposterior sagittal cystotomy has resulted in resolution of incontinence in these instances.

Summary

Most of the complications related to continent catheterizable channels can be resolved by minimally invasive interventions that can be performed by adult general urologists.

Few patients need surgery to revise or replace the channel, and referral to a specialist trained in reconstructive urology would be appropriate in such instances.

Conversion to an incontinent urinary diversion should only be considered as a last resort.

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Augmentation Cystoplasty: Risks for Malignancy and Suggestions for Follow-Up Evaluations

11

Douglas A. Husmann

Introduction

The realization that neoplasia could develop as a consequence of urologic reconstructive procedures first became evident with ureterosigmoidostomy in the 1970s [1, 2]. Specifically, long-term follow-up of patients following ureterosigmoidostomy revealed that approximately 3 % of the patients per decade developed adenocarcinoma of the colon, with another 5 % per decade developing benign adenomatous colonic polyps [1–3]. Interestingly, the site of the malignant lesions and/or adenomatous polyps almost inevitably occurred either at or adjacent to the ureteroenteric anastomosis [1–4]. At that time, it was hypothesized that the development of the neoplastic lesions were dependent on the enteric epithelium employed (colon > ileum), and resulted from chronic inflammation incited by the production of nitrosamines, a known carcinogen, produced from the bacterial breakdown of the fecal, urinary slurry [1–4]. Due to the association of the ureterosigmoidostomy with malignant transformation, the procedure was largely abandoned by the early 1980s. In its place surgeons turned to the alternatives of enteric bladder augmentation or continent urinary reservoirs, surgical procedures that were believed to be free of the risk of carcinogenesis. The reduced risk for carcinogenesis was based on two important assumptions; the absence of the fecal, urinary slurry would prevent the production of nitrosamines and the reliance on ileum as the first choice for use as the enteric component for urologic reconstructive procedures [4–6]. Concern, that this hypothesis was in error arose with the reported development of adenocarcinoma in patients augmented for the contracted bladders arising from tuberculosis and schistosomiasis [5–9]. These random case reports prompted an alternative hypothesis that it was not the chronic inflammatory response arising from the fecal, urinary slurry, but rather, the inflammatory response that is inevitably associated with all forms of urologic reconstructive procedures that would lead to malignant transformation. In particular, it was hypothesized that either the presence of chronic bacteriuria, urine infiltrating into the enteric wall, and or mixed cellular interactions from the juxtaposition of tissues from two disparate origins (intestinal and urothelial) would lead to mutagenic sequence. In essence, the presence of chronic inflammation resulted in the production of toxic oxygen radicals, DNA mutagenesis, and cancer [2, 5–7, 10–14]. This hypothesis appeared to be substantiated when several case reports of malignancy following augmentation for congenital etiologies were published [5, 6, 13, 15–18]. The compilation of the case reports revealed that malignancies in the augmented bladder began to develop about a decade after

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augmentation, presented at a high stage and were associated with poor cancer-specific survival [5, 6, 13, 15–18]. These findings prompted the recommendation that all individuals who had undergone a bladder augmentation, continent urinary reservoir, or enteric neobladder formation for benign urologic conditions, should undergo annual endoscopic and cytologic evaluation beginning 10 years after their surgery. Indeed, concern by some authorities in the field reached high enough levels; they recommended intermittent biopsy of the reconstructed bladder at the time of surveillance [5, 7, 15, 19–22].

Surveillance Protocols: When Is a Protocol Needed and Criteria for Success

Recommendations for annual surveillance procedures, although based on concern for the patient were originally made in the absence of hard facts [7, 15, 17]. Specifically, the need for a recommended surveillance protocol to be successful requires the fulfillment of five crucial criteria. (1) A clinically definable patient population known to be risk for cancer development must exist and the incidence of cancer development in this population must be well established. (2) The cancer if left untreated should be associated with a substantial morbidity and mortality. (3) The cancer needs to have a high prevalence rate at a low stage. (4) Treatment for early stage tumor should have a morbidity and mortality incidence less that the primary disease process. (5) Screening tests should be safe, inexpensive, reliable, and reproducible with a high specificity and sensitivity [3, 20–22].

To determine if a surveillance protocol for bladder cancer in patients undergoing bladder reconstruction is needed and/or can be successful if instituted, will be reviewed below.

Defining the Risk of Malignant Transformation in Bladder Augmentation

The original recommendations for cancer surveillance in patients undergoing bladder augmentation or neobladder formation for benign conditions were based on two important assumptions. First, the compilation of case reports in patients suggested that this population was at risk for cancer development. Second, it was believed that the underlying bladder dysfunction that resulted in the need for bladder augmentation or neobladder formation was not associated with an increased risk of malignancy [7, 15, 17]. Significant concern regarding this hypothesis arose, due to the poorly defined risk of malignant transformation in patients with abnormal bladders not undergoing bladder augmentation. Specifically, the incidences of malignant transformation in patients with bladder dysfunction due to primary underlying disease process (i.e., exstrophy–epispadias complex, posterior urethral valves, and neurogenic bladders) were either poorly described or unknown [11, 12, 18, 23–28]. Adding to this conundrum was the finding that almost all published case reports failed to assess the possibility of exposure of the patient to tobacco, immunosuppression, and/or concurrent viral cystitis all known carcinogens [18, 27, 29–33]. They also failed to access the risk of cancer arising due to the underlying disease process that was responsible for the need for a bladder augmentation or neobladder [3, 18, 23–27, 29–32].

In an attempt to answer the question regarding whether bladder augmentation is an independent risk factor for bladder cancer in patients Higuchi et al., performed a prospective cohort study with a matched control population (matched for age, sex, and the same underlying bladder abnormality). Patients had undergone bladder augmentation for management of the congenital abnormalities, including exstrophy–epispadias complex, posterior urethral valves, and neurogenic bladder arising from spina bifida. In this case of matched controlled study they noted no difference between the two populations [18]. Specifically, risk for the development of bladder malignancy with patients undergoing an augmentation with either ileum or colon was approximately 1.5 % per decade, compared to the incidence of 0.9 % per decade in case matched controls who had not undergone a bladder augmentation, $p = 0.55$ [18]. These findings suggest that individuals with an underlying bladder abnormality arising from any congenital cause, are at a threefold to fourfold increased risk for the development of a bladder malignancy

compared to the incidence of bladder cancer reported in the normal US population. This risk was similar whether or not they had undergone a bladder augmentation [18, 34]. It is critical, however, to point out that this data involves only individuals undergoing augmentation with ileum or colon. Substantial concerns arise regarding two specific populations that have undergone bladder augmentation. First, long-term follow-up of patients undergoing an augmentation confirms a hypothesis first advanced by Dr. Ruben F. Gittes, that the segment used for augmentation may impact the incidence of malignancy [4]. In particular, it has become apparent that augmentation with a gastric augment results in gastric atrophy of the augmenting segment, a premalignant condition [5, 17, 19, 35–37]. Indeed, gastric cystoplasty appears to be associated with twice the risk of an ileal or colon augment, 2.8 % per decade compared to 1.5 % per decade [5, 6, 13, 17]. Second, we are concerned regarding the incidence of bladder cancer in immunosuppressed patients. These individuals are not only exposed to the known carcinogenic effects of immunosuppression but are also at an increased risk for the risk of carcinogenesis arising from viral cystitis (EBV, BK, or CMV viruses) [3, 18, 27, 29–32]. These two particular patient populations appear to be at sixfold to tenfold increased risk for malignancy [17, 18, 27, 29, 32, 34, 38]. In essence, as data has accumulated over the decades, patients with bladder augmentations by ileum or colon are at no higher risk for malignant transformation than a patient population with the same underlying bladder abnormality, both, however, are at an increased risk of cancer development than the normal population. Of significant concerns are individuals undergoing bladder augmentation with gastric segments or individuals with augments exposed to immunosuppressive agents especially if they have a concurrent history of viral cystitis.

Natural History of Cancer Within a Bladder Augment

Exactly how aggressive are tumors arising in abnormal bladders? Can we diagnose these tumors at a low stage? When we compare patients with congenitally abnormal bladders to the normal patient population, approximately 4–6 % of patients with congenitally abnormal bladders with or without an ileal or colonic bladder augmentation will develop a malignancy by the sixth decade of life [18]. Approximately 80 % of whom will have locally invasive (T2 or higher) and/or metastatic disease at the time of presentation [18]. Cancers arising in these congenitally abnormal bladder either with or without an ileal or colonic bladder augmentation are associated with a cancer-specific mortality of >80 % (median of 1.5 years) from the time of diagnosis and a very low incidence of survival [18, 34]. Of particular interest are a series of case reports where routine surveillance cystoscopy was normal 3–18 months prior to the diagnosis of metastatic cancer arising from the augment. All cancers in these five patients were fatal despite a normal cystoscopic evaluation just months prior to the diagnosis of widely metastatic disease [5, 15, 17, 18, 21, 25]. These findings suggest that either the tumors have a rapid malignant potential and/or that cystoscopy is inadequate to identify tumor within this patient population. Compare the findings reviewed above to the incidence of bladder malignancy arising in the nonsmoking US population without a congenital bladder abnormality. In this patient population, 2 % of the individuals will develop a bladder tumor by the eighth decade of life, approximately 80 % of whom will have <T2 disease at the time of diagnosis [3, 18, 34]. The compilation of the published findings is highly suggestive that individuals with a primary bladder abnormality with or without an augment are at an increased risk for bladder malignancy. Indeed, histopathologic, molecular, and genetic studies of these cancers show that they are a distinct clinicopathologic variant that is extremely aggressive, with rapid growth, high metastatic potential, and high cancer-specific death rates [18, 39]. While the cancer does fulfill the second criteria needed to establish a successful screening protocol, tumors left untreated are associated with a substantial morbidity and mortality [3, 18, 34, 39], it does not meet the third criteria, a high prevalence of the tumor at a low stage when they are amenable to minimally invasive treatment [3, 22].

Cystoscopy, urine cytology, and bladder biopsy: are they reliable, reproducible with a high specificity and sensitivity?

While molecular (e.g., FISH) testing is becoming a mainstay of bladder cancer surveillance, only cystoscopy and selective cytology are currently recommended for routine evaluation of microhematuria/hematuria in the general population (AUA Guidelines: microhematuria-2012, bladder cancer-2007). As previously discussed, multiple authors originally encouraged the use of cystoscopy and cytology for routine annual screening of patients with bladder augments [5, 7, 15, 19, 20]. Although the intent was pure, the recommendations were made without verifying that both the disease process and the screening methodologies recommended met the fifth requirement necessary for the implementation of a successful surveillance protocol (screening tests should be safe, inexpensive, reliable, and reproducible with a high specificity and sensitivity). Problems first became evident with the use of urine cytology in the presence of enteric epithelium. Exfoliated enteric epithelial cells that are exposed to and then maintained for prolonged time period in urine i.e., urine obtained from augmented bladders and urinary reservoirs, can degenerate into clusters that resemble urothelial carcinoma, leading to a high false positive rate [22, 40]. It has also been noted that the chronic pyuria and intermittent catheterization, ubiquitously present in this patient population can cause cellular atypia including increased nuclear-to-cytoplasmic ratio, nuclear atypia, and papillary aggregation, all changes diagnostic for urothelial cancer [3, 22, 40–44]. Our personal experience with following 65 patients with an augmented bladder with yearly cytology over a 12-year period, revealed a false positive rate of 10 %. The specificity of urine cytology for our patient population was 90 % compared to 99 % in a nonaugmented patient population under surveillance [22]. The sensitivity of urine cytology in the augmented patient could not be determined, since no patient under this protocol developed a tumor [22]. It is also noteworthy that the abnormal urine cytology prompted several unnecessary CT urograms and random bladder biopsies [22]. We subsequently abandoned the routine use of urine cytology due to both its cost ($450 at our institution) and its motivation to prompt us to do more costly, invasive, and potentially nephrotoxic tests in a population already at high risk for renal insufficiency.

What about routine endoscopy? To determine if this test would be beneficial, two items are key; we must establish the incidence of the disease and the ability of endoscopy to diagnose low-stage disease. First as previously noted the incidence of malignancy developing in this patient population is 1.5–2.8 % per decade [3, 5, 6, 17–19]. In essence, a urologist would have to perform >950 cystoscopies to diagnose one bladder tumor. At approximately $600 per cystoscopy, the cystoscopic costs alone would be approximately $570,000 to diagnose one bladder tumor. This estimate presupposes that surveillance cystoscopy is accurate in identifying early stage tumors, which evolving evidence suggests against [5, 15, 17, 18, 21, 25]. Specifically it should be noted that routine cystoscopy used for tumor surveillance in the nonaugmented patient population has a median sensitivity of 65 % and specificity of 71 %, we would expect this sensitivity and specificity to be lower in the patient with a augmented bladder where multiple folds and crevices of the enteric epithelium are the norms [45–48]. In addition to the low sensitivity and specificity, as we have noted previously there is no guarantee that cystoscopy will identify a low-stage bladder tumor amenable to resection prior metastasis, due to the rapid growth potential of these tumors [3, 15, 17, 18, 21, 22, 25, 39].

What about routine bladder biopsy? Dr. Rizwan Hamid and associates documented the poor reliability of this test, in their patients, ($N=92$ undergoing surveillance >10 years following augmentation) routine biopsy of the enteric segment, anastomotic line, and native bladder; no biopsy was positive for malignancy [21]. One patient presenting for follow-up did note hematuria and biopsy revealed a metastatic neuroendocrine tumor which resulted in cancer-specific death within 3 months of diagnosis. It is noteworthy that this patient had a normal surveillance cystoscopy 18 months prior to her presentation with metastatic disease [21]. Based on these

findings Hamid and associates recommended against routine endoscopy or biopsy unless a patient was symptomatic [3, 21, 22].

Can we establish a successful routine screening protocol for cancer development in patients with a bladder augment or congenitally abnormal bladder known to be at risk?

Due to the low event rate of malignant transformation, poor sensitivity for cytologic screening, lack of proven benefit for annual cystoscopy to diagnose low-stage malignancy in the presence of highly aggressive tumor, combined with a cost-ineffective screening methodology, there does not appear to be any benefit in the routine use of annual screening exams for the onset of malignancy [3, 18, 22]. However, long-term follow-up of this patient population serves a multitude of purposes; including preservation of renal function, prevention, and treatment of renal and bladder calculi, confirmation that metabolic or nutritional abnormalities have not developed and verification of compliance with medical directives [3, 18, 22]. The follow-up recommendations we currently follow are based on the need for annual follow-up on this population, they are not based solely on malignant concerns, but rather to prevent the morbidities associated with augmentation or continent urostomy formation. We start this evaluation by on obtaining an interval medical history focused on determining whether baseline urological symptoms have changed, obtaining baseline serum chemistry and evaluating whether there are new radiologic findings [3, 22]. See Fig. 11.1.

Is there a need for cystoscopic surveillance in specific patient categories, e.g., patients following gastric augmentations, or patients with a history of bladder augmentation following renal transplantation?

The published literature strongly suggests that individuals undergoing a gastric augmentation (2.5-fold increased risk) and individuals with a history of bladder augmentation undergoing a renal transplantation (sixfold to tenfold increased risk) have a significantly higher risk of developing a malignancy compared to an individual

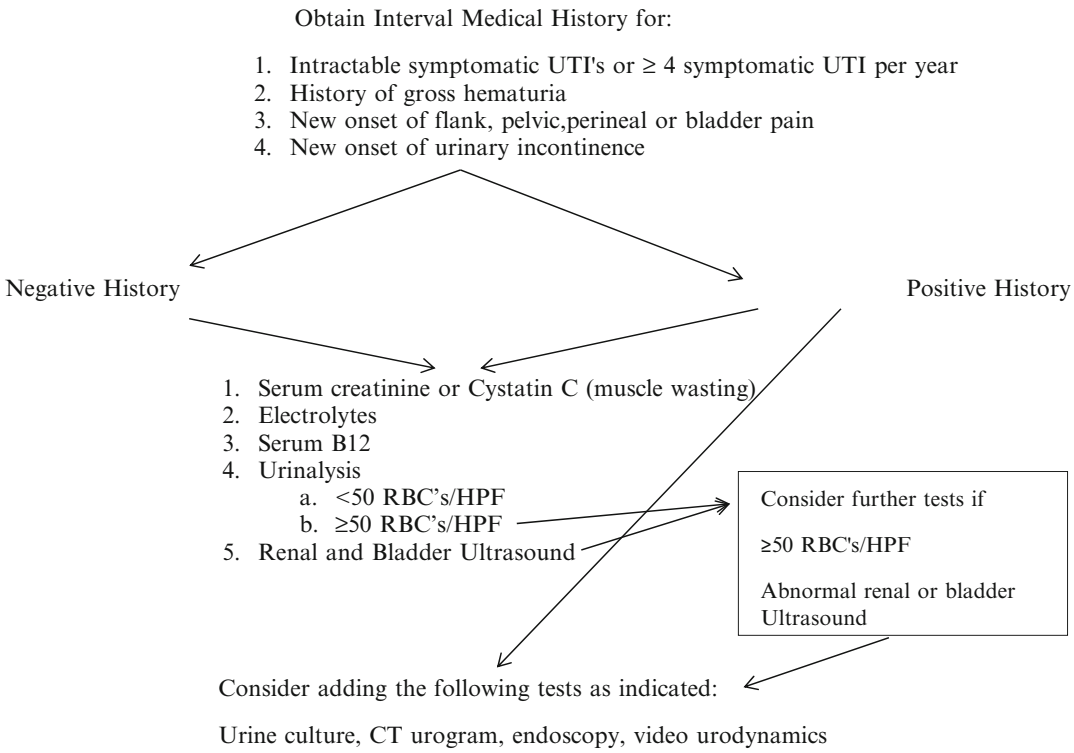

Fig. 11.1 Follow-up of bladder augmentations and neobladder formation after reconstruction for benign urologic conditions

undergoing a augmentation without this surgical history [17, 18, 27, 29, 32, 34, 38]. In view of these findings the question arises should we routinely place these select patient populations under cystoscopic surveillance? Although we would strongly recommend that we routinely follow these individuals on an annual basis on the protocol outlined above, we do not alter our routine surveillance protocol to include annual cystoscopy for these specific patient populations. This recommendation is based on the hypothesis that routine cystoscopic surveillance would not meet the definition of a successful surveillance protocol, due to the aggressive nature of the primary malignancy and the low sensitivity and specificity of cystoscopy [3, 15, 17, 18, 21, 22, 25, 39].

Conclusion

Annual screening endoscopy and cytology in patients with bladder augmentation or continent urostomy for congenital urological disease is not recommended due to their poor sensitivity, unproven specificity, cost-ineffectiveness, and inability to diagnose a low-stage malignancy. Surveillance of this patient population is, however, recommended to prevent the associated serious complications that can lead to upper urinary tract destruction, metabolic, and vitamin derangements following these procedures. The onset of new clinical symptoms and/or abnormal serial baseline serum chemistries or radiographic findings, should, when indicated prompt further evaluations to rule out the possibility of tumor development.

Summary

- Neuropathic bladder with or without augmentation poses a fourfold to sixfold increase in bladder cancer risk compared with the general population.
- Lethality of cancers seen in neurogenic bladder is worse than the general population, with 80 % demonstrating locally invasive (T2 or higher) and/or metastatic disease at the time of presentation.
- Median survival from diagnosis is 1.5 years.
- Risk of malignancy in augmentation cystoplasty:
  - Gastric cystoplasty 2.8 % per decade.
  - Colon or ileal cystoplasty 1.5 % per decade.
- Renal transplantation with history of viral cystitis represents a very high risk group (sixfold to tenfold increase).
- Despite elevated risk, routine cytology, FISH, and cystoscopy are not recommended, as sensitivity of determining malignancy is very poor and cost of these tests are high.
- Recommended annual surveillance:
  - Interval medical history focused on determining whether baseline urological symptoms have changed.
  - Serum chemistries.
  - Radiographic screening (ultrasound, KUB, or CT when indicated).
- Abnormalities seen on annual surveillance should prompt further diagnostic testing as appropriate

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BPH and Pelvic Organ Prolapse in Patients with Neurogenic Bladder

12

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Introduction

The successful management of many diseases that result in neurogenic bladder has allowed patients who were previously only cared for by Pediatric Urologists to live well into adulthood. In the past, patients with myelomeningocele and neurogenic bladder rarely used to live into their third decade. It is now not uncommon for these patients to live significantly longer lives [1]. With this increased longevity comes the myriad of adult Urologic conditions that these patients are now beginning to face, including benign prostatic hyperplasia (BPH) and pelvic organ prolapse (POP). While BPH and POP are common urologic conditions in the general adult population, they present a unique challenge for patients with neurogenic bladder, and relatively little is known about the effects of these disorders in this patient population. This chapter aims to focus on the presentation and management of patients with neurogenic bladder who develop BPH or POP in their adult lives.

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Transition of Pediatric Patients with Neurogenic Bladder into Adulthood

The management of neurogenic bladder in childhood depends upon a number of underlying factors, including the dexterity and ability of a patient to perform catheterization or void by Valsalva maneuvers, the etiology of bladder dysfunction, and prevention of adverse sequela such as renal deterioration [2–5]. In a patient with both good manual dexterity and the willingness to catheterize through his or her native urethra, oftentimes clean intermittent catheterization (CIC) presents the most manageable form of bladder decompression [2]. Voiding by Valsalva maneuver also allows many patients with incompetent urethral sphincters to empty their bladders well, without the need for catheterization [6]. In the patient who is unable to catheterize or void by Valsalva, and for whom the concern of renal deterioration, urinary tract infections, pain from frequent urethral catheterization, or reliance on another individual exists, often a urinary diversion procedure such as a Mitrofanoff or Monti-Yang procedure may be performed and allows a greater quality of life in these patients [7, 8].

Until recently, most patients with neurogenic bladder have relied upon the care of Pediatric Urologists for management due to their familiarity with the disease process and previous surgeries, and lack of knowledge of these conditions by adult urologists. Conversely, pediatric urologists

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are less adept at dealing with the adult urologic conditions that develop in these patients, including malignancies, BPH, and POP. These adult onset urologic issues may present problems in these patients such as difficulty with self or assisted catheterization, issues with voiding by previously acceptable Valsalva maneuvers, and hematuria to include a few dilemmas. Thus, the need to be managed by a practitioner with knowledge of each of these conditions is especially relevant to the aging adult patient with congenital neurogenic bladder.

Patients with Neurogenic Bladder Who Develop BPH or Pelvic Organ Prolapse

Patients with neurogenic bladder typically become accustomed to managing their disease in a certain way. They become comfortable with self-catheterization or Valsalva voiding and are usually fairly happy with the management of their disease. With advancing age and the development of either BPH or POP, which may cause difficulties with these particular management strategies, distress can occur. It may be difficult for practitioners, as well, to determine the etiology of increasing difficulty with a previously effective management strategy. For example, in a 60-year-old male patient with an acontractile neurogenic bladder who has performed CIC for a number of years, does the development of pain and difficulty with catheterization indicate the formation of a stricture or an enlarging prostate? In the aging male who previously did not have difficulty voiding and who empties his bladder well, the development of lower urinary tract symptoms (LUTS) is more likely to signify bladder outlet obstruction from BPH. Similarly, in a 20-year-old male with a neurogenic bladder who routinely performs CIC and develops difficulty with catheterization, stricture formation from chronic catheterization is favored over development of BPH. Similar problems may arise in female patients who void by Valsalva and later develop POP. In these patients, does progressive difficulty voiding signify obstruction from POP or failure to produce adequate intra-abdominal pressure in order to void to completion? Numerous other problems may arise as well, including formation of mucous in augmented bladders [9–11], formation of bladder stones [12, 13], and renal deterioration [14–16]. Weight gain and increased disability associated with aging in the myelomeningocele population may result in increased difficulty accessing the urethra for CIC, particularly in the female patient who is wheelchair-bound and/or the male patient with a buried penis. This often results in management with an indwelling Foley catheter, a solution that predisposes to fistulae, leakage, ulcers, and infections, and should never be utilized as a long-term bladder management solution. All of these obstacles are best managed by a urologist with expertise in these conditions, yet with knowledge of the past surgeries and management of patients with neurogenic bladder.

Presentation and Management of Patients with Neurogenic Bladder Who Develop BPH in Adulthood

Background

Previous studies have demonstrated that prostate growth occurs at a rate of approximately 0.6–2.5 cm^3 per year in men over the age of 30, corresponding to an increased volume of roughly 2.5 % per year. In these studies, the highest rate of growth occurred between the ages of 56–65, and then declined for older men [17, 18]. Increased prostate size has implications for men with neurogenic bladder for a number of reasons, including higher residual amounts of urine in men who void by Crede or Valsalva maneuvers, increased pain and difficultly in performing catheterization in men who are managed by CIC, and higher rates of urinary tract infections. In general, men with BPH commonly present with LUTS such as urinary urgency, frequency, hesitancy, nocturia, a weak urinary stream, and feelings of incomplete emptying [19]. In men with neurogenic bladder who void by Valsalva or Crede maneuver, many of these symptoms can be the initial presenting complaint.

Evaluation

In general, in patients with neurogenic bladder who present with complaints suspicious for BPH, a thorough history and physical exam should be completed. A digital rectal exam should be performed to assess the size and shape of the prostate [20]. Concerns for prostate cancer, including a history of weight loss, nodularity on digital rectal exam, and a rising PSA should be managed in the usual manner for workup of prostate cancer, including a PSA test if not already done, and a prostate biopsy when indicated. If the patient is usually able to void by himself, initial evaluation should include a voiding diary and a post-void residual (PVR) volume. Urodynamic evaluation should also be undertaken, both for initial evaluation and when urinary symptoms or PVR change. An assessment of renal function should also be checked annually, although the optimal method of measuring renal function in this select subset of patients remains to be established (reference Kaufman chapter). A urinalysis should be obtained to screen for infection (if the patient is symptomatic), medical renal disease, and glucosuria. If warranted, a urine culture should be sent. Imaging should include a renal ultrasound to evaluate for hydronephrosis in order to assess for upper urinary tract impairment. Urine cytology should be obtained if there is a concern for malignancy, and a cystourethroscopy should be performed to evaluate the urethra for strictures, the prostate for contour and enlargement, and the bladder for evidence of trabeculation or tumors. In patients with diabetes, an assessment for peripheral neuropathy should be performed as hyperglycemic nerve damage may lead to worsening detrusor function [21].

In patients with an atonic, high-pressure, or augmented neurogenic bladder who perform intermittent catheterization, the initial indication that BPH has developed most likely will manifest as difficulty with catheterization [22, 23]. Men will report that they feel it is increasingly difficult to pass a catheter into the bladder while using catheters that previously passed smoothly. A thorough history will elicit that this developed over time, and many men may not present until significant difficulty with catheterization occurs. This undermines the importance of close follow-up in all patients with a neurogenic bladder, but even more so in those who perform CIC. Additionally, patients may present with hematuria, either spontaneous or in combination with catheterization [24, 25]. This is due to the increased size of the prostate and neovascularity of the enlarged gland [26]. When patients present in this way in particular, urothelial malignancy must be ruled out (see Chap. 11).

Complications of BPH and difficulty with catheterization in patients with an atonic, high-pressure, or augmented bladder include prostatitis, urinary tract infections, renal deterioration from increased bladder residual urine volumes, hematuria, and bladder rupture in patients with augmented bladders. In some cases, urinary tract infections and prostatitis may be the initial manifestation that a man is experiencing difficulty with catheterizations. In rare circumstances and in patients with poor follow-up, renal failure or bladder rupture may be the reason for initial presentation.

Workup in these patients should include a thorough history and physical exam with emphasis on the digital rectal exam, as well as laboratory assessment of creatinine in patients for whom there is a concern for renal deterioration [27]. Imaging studies, when indicated on the basis of history and physical, may include a transrectal ultrasound to assess the size of the prostate, a renal ultrasound to evaluate for hydronephrosis, and in some cases a CT scan of the abdomen and pelvis, for example if a concern for urinary tract malignancy exists. A urinalysis and urine culture should be obtained if prostatitis or a urinary tract infection is suspected. Finally, a cystourethroscopy should be performed to assess for urethral stricture and to examine the contour of the prostate [28]. In patients for whom a CT Urogram is contraindicated, such as in patients with renal impairment and elevated creatinine, but for whom evaluation of the upper tracts is necessary, a retrograde pyelogram performed at the time of cystoscopy is an acceptable alternative to CT Urogram.

In a patient with neurogenic bladder who voids by Valsalva maneuvers, a common initial presentation may be the feeling of incomplete

emptying, a weaker stream than usual, or a complete inability to void. Patients who void by Valsalva or Crede maneuver have an increased residual urine volume initially, and if BPH develops, the volume of residual urine may increase. This can lead to renal impairment secondary to higher pressures, renal and bladder stones, and hydronephrosis [29].

Patients with neurogenic bladder who void by Valsalva or Crede maneuvers that present with complaints suspicious for BPH should initially have a thorough history and physical exam performed with emphasis on the prostate exam and International Prostate Symptom Score [30]. Prostate volume should be estimated by digital rectal exam. These patients should additionally have a PVR checked as well as serum creatinine. Renal and bladder ultrasound should be performed in any patient for whom renal impairment or renal and bladder stones are suspected. This is especially imperative in patients who have high-pressure neurogenic bladders, as increased pressure from urinary retention can cause severe upper tract impairment [31]. Urodynamic evaluation should also be performed and compared to previous urodynamic testing for the evaluation of bladder pressures, maximum flow rate, and residual urine volume. A cystourethroscopy should be performed if there is any concern for urethral stricture or urothelial malignancy, and in cases in which surgical intervention is planned.

Management strategies in patients with atonic, high-pressure, or augmented neurogenic bladders who perform CIC should aim to preserve renal function, reduce the risk of urinary tract infections and sepsis, maintain dryness, and preserve a good quality of life for patients. In many patients who have enjoyed a good quality of life with CIC, their preference may be to continue a regimen of catheterization. Initial consideration should be given to medical therapy with an alpha-blocker alone or in combination with a 5-alpha reductase inhibitor to reduce the size of the prostate, decrease LUTS, and allow for continued catheterization. Medical management with alpha-blockers and 5-alpha reductase inhibitors has been shown to reduce the risk of clinical BPH progression and reduce BPH symptomatology [32–34]. In patients for whom medical therapy is contraindicated or fails, other options include an indwelling suprapubic catheter, formation of a catheterizable channel (Mitrofanoff), and surgery to reduce the size of the prostate.

It may be tempting to utilize an indwelling Foley catheter as a solution in patients who do not wish to undergo surgery or who are medically unfit, however, the authors caution that this solution invariably leads to greater problems, including clinically significant urinary tract infections, bladder stones, urethral erosion, and in some patients, ongoing discomfort and pain [35–37]. Alternatively, the patient may choose to have a suprapubic catheter placed for bladder decompression. Advantages to this over an indwelling urethral catheter include the ability to obtain bladder decompression in patients for whom passage of a urethral catheter is difficult or impossible, less pain during catheter changes, decreased rates of UTIs, and decreased rates of urethral erosion, and sphincter damage. Disadvantages of a suprapubic tube include the risk of injury to other structures such as bowel during initial placement of the suprapubic tube, risk of dislodgement with transferring from a chair, stone formation, malignancy, and urinary tract infections.

In patients who are deemed to be good surgical candidates and who wish to continue to perform intermittent catheterization, different outlet procedures allow reduction in the size of the prostate and channel opening, thereby permitting continued catheterization [28]. Both transurethral resection of the prostate and laser vaporization of the prostate allow a minimally invasive approach to opening the prostatic urethra. Other procedures such as transurethral microwave thermotherapy and transurethral incision of the prostate may be attempted for small glands, with the realization that further procedures may be necessary. In very large prostate glands in patients who have not had their bladders augmented, open and robotic simple prostatectomy may be considered as well as newer procedures such as Holmium laser enucleation of the prostate (HOLEP). A simple prostatectomy should not be performed, however, in patients who have had their bladders augmented

due to the risk of injury to the reconstructed bladder. It is important to consider positioning for patients being considered for office procedures, as central obesity and contractures of the lower extremities may hinder positioning of a patient in lithotomy and baseline cardiopulmonary disease may impair the ability of the patient to lay supine. For such patients, general anesthesia should be considered.

Management of patients with neurogenic bladder who void by Valsalva and who develop BPH is multifaceted. Initial attempts at medical management may be attempted with an alpha-blocker alone or in combination with a 5-alpha reductase inhibitor [32–34]. In patients who do not experience relief of symptoms with medical therapies, further management may include a regimen of CIC or surgeries to open the prostatic urethra, such as TURP or laser vaporization of the prostate. Prostatectomy should be considered in patients with very large prostate glands.

Special consideration must be given to patients with high-pressure neurogenic bladders on anticholinergic therapy that develop BPH. The increased outlet resistance in combination with an anticholinergic can lead to elevated residual urine volumes and urinary retention, as well as decreased urinary flow rates [38, 39]. The goal of preventing retention and increased upper tract pressures should take precedence in these patients, and may necessitate continuous bladder drainage with an indwelling urethral catheter while a decision is made for definitive treatment. While a suprapubic tube offers a definitive management strategy that is acceptable for many patients, in some it may fail due to the formation of stones, leakage around the tube, or recurrent infections. Supravesical diversion, such as an ileal conduit, may present a definitive option in these patients. This form of management, however, incurs its own set of risks, which may include more substantial perioperative complications (e.g., wound infections, small bowel obstructions, and a greater perioperative mortality), as well as parastomal and incisional herniae, though this solution provides an option that ultimately results in a dry perineum and removes a foreign body from the inside of the bladder.

Presentation and Management of Patients with Neurogenic Bladder Who Develop Pelvic Organ Prolapse in Adulthood

Background

In women with neurogenic bladder who enjoy a good quality of life through CIC, POP can cause a significant amount of stress and bothersome symptoms. Studies have shown that up to 50 % of American women may develop prolapse, and between 2.9 and 6 % of them will be symptomatic [40–42]. Most women with uterine prolapse, cystocele, enterocele, or rectocele simply report a sensation of their pelvic organs falling out of the vagina. More severe cases can lead to urinary or fecal incontinence, urinary retention, or significant difficulty defecating [43]. Specifically in women with neurogenic bladder who perform CIC, they may report increasing difficulty with catheterization due to a prolapsed uterus or cystocele.

While patients with neurogenic bladder who perform CIC and develop POP usually report difficulty with catheterization, their initial presenting complaint may be urinary incontinence between catheterizations, the feeling of fullness sooner after performing catheterization, or the need to catheterize more frequently. This is especially relevant for patients with high-pressure neurogenic bladders.

Evaluation

It is important to elicit a good history and perform a thorough physical exam in any woman with neurogenic bladder who previously performed CIC with ease, as oftentimes the embarrassment associated with POP may prevent these women from readily disclosing their full symptomatology. Workup for patients with neurogenic bladder normally managed by CIC who present with POP should include a urinalysis and urine culture in all patients who report a history of dysuria and in patients with urinary incontinence in order to rule

out a urinary tract infection. A creatinine should be obtained and compared to the patient's baseline creatinine. Additionally in these patients, a renal ultrasound should be performed to evaluate for hydronephrosis or upper tract damage.

Many of the same complaints in women with neurogenic bladder who perform CIC and develop POP are reported in women with neurogenic bladder who void by Valsalva maneuvers and develop POP. These include the sensation of incomplete emptying, progressive difficulty voiding, the need to urinate more frequently, post-void dribbling of urine or incontinence between voids, and the sensation that something is protruding out of the vagina. In these women, however, it is important to recognize the symptoms of difficulty voiding by Valsalva maneuvers because unrecognized retention in these patients could lead to renal deterioration.

Workup of patients with neurogenic bladder who void by Valsalva or Crede maneuvers and in whom POP is recognized begins with a PVR to assess for urinary retention. If retention is suspected or confirmed, a renal ultrasound should be performed to assess for hydronephrosis and upper tract damage. Though this may be technically difficult to perform in these patients due to size, paraplegia, and lower extremity contractures, it is important to assess for these complications when retention is recognized. Additionally, serial measurement of renal function should be obtained to assess for deterioration. Finally, a urodynamic study to assess voiding pressures, urinary flow rate, and bladder capacity may be considered, especially if surgery to correct the prolapse is considered [44].

Treatment

In patients who develop POP and who are still able to reliably catheterize without difficulty, conservative management may be attempted initially, as recommended by both the American College of Obstetrics and Gynecology Committee on Practice Bulletins and the Agency for Health Care Policy and Research [45]. In patients with low-grade cystocele, rectocele, or uterine prolapse and in whom catheterization is still relatively easy to perform, it may be advisable to simply continue on a regimen of CIC. In patients for whom symptoms are more bothersome, another conservative management strategy might be placement of a pessary. Many women have reported good relief of their symptoms with a pessary alone, and this may be an acceptable management strategy in many women with neurogenic bladder [46].

In patients with a high-grade cystocele, rectocele, or uterine prolapse, or in whom catheterization has become more difficult, surgical options may need to be explored. In patients who have developed a high-grade cystocele or who are having significant difficulty with catheterization because of a cystocele, an anterior colporrhaphy allows for reduction of the cystocele and greater ease of catheterization. In patients who have developed a uterine prolapse and are having difficulty with catheterization, surgical options include hysterectomy in women past childbearing age and a sacrohysteropexy in women who have not undergone menopause or who wish to retain their uterus. This can be done transvaginally or transabdominally (frequently laparoscopic/robotic). In women who have developed difficulty with catheterization because of a rectocele, posterior colporrhaphy provides the best means of long-term success and patient satisfaction.

Treatment of POP in patients with neurogenic bladder who void by Valsalva maneuvers is very similar to that in patients who perform CIC. Conservative management should be attempted first, especially in patients who are still able to void reliably well, followed by placement of a pessary in patients with a low-grade POP or in patients who are unfit to undergo surgery or do not wish to undergo a surgical procedure. Anterior colporrhaphy is the preferred surgical management for patients with a high-grade or bothersome cystocele, as is posterior colporrhaphy for patients with a high-grade or bothersome rectocele. Sacrohysteropexy may be attempted for patients with uterine prolapse who do not wish to undergo hysterectomy, and a hysterectomy may be considered in patients with uterine prolapse who have completed childbearing.

Quality of Life

The main goals in patients with neurogenic bladder who void by either CIC or Valsalva maneuvers and develop BPH or POP in adulthood include preservation of renal function, reducing urinary tract infections, and maintenance of a good quality of life. This may be accomplished via regular follow-up and monitoring of important parameters such as serum creatinine, PVR urine volume, and urodynamic testing. Most patients who enjoy a good quality of life through regular CIC or Valsalva voiding may continue to do so even after the development of BPH or POP. Strategies to manage these diseases range from simple conservative measures such as medical BPH management and pessary placement in patients with POP, to surgical approaches including prostatectomy and colporrhaphy or hysterectomy with prolapse repair. Risks of the various treatment options must be considered and weighed against their benefits, with more conservative approaches being favored initially.

Summary

Patients with neurogenic bladder who either perform CIC or void by Valsalva maneuvers represent a unique population of patients who are increasingly beginning to experience the myriad of adult urological problems.

In these patients who develop BPH, therapy should aim to preserve renal function and minimize distress and pain by continued bladder decompression. This may include medical therapies to reduce the volume of the prostate, such as alpha-blockers and 5-alpha reductase inhibitors, to transurethral resection of the prostate and surgical prostatectomy.

In patients with neurogenic bladder who develop POP, goals of therapy should also include preservation of renal function and ease of bladder decompression. This may be accomplished by conservative measures including pessary placement or surgical options including anterior and posterior colporrhaphy or hysterectomy with prolapse repair.

Care should be managed by a urologist with knowledge of both pediatric urologic disease and their adult analogue.

Summary and Best Practice Recommendations

- In a patient with neurogenic bladder and both good manual dexterity and the willingness to catheterize through his or her native urethra, oftentimes CIC presents the most manageable form of bladder decompression.
- In patients with neurogenic bladder who perform CIC, the initial indication that BPH or POP has developed may be difficulty with catheterization.
- In patients with neurogenic bladder who void by Valsalva maneuvers, a common initial presentation of BPH or POP may be the feeling of incomplete emptying, a weaker stream than usual, or the complete inability to void.
- Unique to patients with neurogenic bladder who develop POP, the initial presentation may be incontinence between catheterizations, the feeling of a full bladder sooner after performing catheterization, or the need to catheterize more frequently.
- The recommended workup for a patient who presents with difficulty catheterizing or voiding by Valsalva includes a urinalysis, creatinine, renal ultrasound, and consideration of urodynamic testing. If concern for a stricture exists, cystoscopy should be considered.
- Initial management for patients with neurogenic bladder who develop BPH should be with medical therapy, consisting of an alpha-blocker alone or in combination with a 5-alpha reductase inhibitor. In patients for whom medical therapy is contraindicated or fails, other options include an indwelling suprapubic catheter, formation of a catheterizable channel

(Mitrofanoff), and outlet procedures to reduce the size of the prostate.

- Management in patients with neurogenic bladder who develop POP should be based on patient preferences, and may include measures such as anti-incontinence pads, placement of a pessary, or repair of the prolapse.

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Posterior Urethral Valves in Adolescents: Clinical Problems, Management, and Follow-Up

13

Dev Mohan Gulur and Andrew D. Baird

Background

Posterior urethral valves (PUV) was first described by Morgagni, but defined and classified by Hugh Hampton Young in 1919 [1–2]. PUV accounts for 9 % of the antenatally detected obstructive uropathy [3]. It is a congenital condition affecting 1:3,000–8,000 live male births [4]. The aetiology of PUV is unknown.

The pathophysiology of PUV involves multiple organs as below:

1. Lung: Pulmonary hypoplasia
2. Kidney: Renal insufficiency due to glomerular injury and dysplasia
3. Tubular: damage can cause nephrogenic diabetes insipidus resulting in polyuria
4. Ureter: Impaired contractility can cause chronic hydronephrosis
5. Bladder: Hypercontractile, unstable, low compliance, and eventually myogenic failure

PUV is frequently diagnosed on antenatal and postnatal ultrasound scans but the defining diagnostic test is the micturating cystourethrogram (MCUG). Initial management is insertion of a urethral catheter in the infant to relieve the obstruction, rehydrate, treat sepsis, and manage renal failure before considering transurethral ablation of the PUV when the infant is stabilized. In some infants who are very premature and deemed to be small for transurethral ablation, suprapubic vesicostomy and cutaneous ureterostomy are useful temporizing options bearing in mind that cutaneous ureterostomy carries the risk to the bladder of developing severe, irreversible hypertonicity [5]. The role of vesicoamniotic shunting has not been decisively shown to be of benefit [6].

Long-term sequelae of PUV include risk of renal failure and bladder dysfunction which makes lifelong follow-up of these children imperative. In a small subset of patients, Duckett suggested pop-off mechanisms which result in better preservation of renal function in the long term [7]. Pop-off mechanisms include renal pelvic or bladder rupture with urinary ascites, large bladder diverticulum, patent urachal sinus, or significant VUR with a nonfunctioning ipsilateral kidney. This chapter specifically looks in to the impact of PUV in adolescence and adulthood.

Renal Impairment and Failure

A third of patients with PUV will develop end-stage renal disease (ESRD) during childhood or young adulthood despite active treatment [8, 9] progressing to transplant in 15.8 % of children [10]. Warshaw et al. in their study of 22 patients found that more than half of patients developed

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renal failure either in infancy or in adolescence [11]. They observed that renal dysplasia plays a predominant role in the early onset of renal failure. Lal et al. in their study of 84 patients treated for PUV and followed up for 1–21 years found that 60.5 % of them had maintained normal serum creatinine values through adolescence and adulthood, and in particular 14.3 % of them had developed chronic renal failure (CRF) between the ages of 12 and 18 years [9]. Very few long-term studies exist to present true prevalence of need for renal replacement therapy or transplant in middle and later adulthood owing to the lack of consistency of databases beyond pediatric life.

Hyperfiltration injury due to the increased physiological demands during puberty is postulated to be one of the causes of renal function deterioration, and proteinuria is a very good indicator of impending CRF [12]. Jnakinen et al. have shown that there is a negative impact on Quality of Life (QoL) particularly in children with renal insufficiency due to PUV [13].

Detrusor Dysfunction

There is data to suggest that children with PUV have a twofold to threefold risk of developing lower urinary tract symptoms (LUTS) as adults [14]. Mitchell coined the term "valve bladder" in 1982 to describe the phenomenon of obstruction to the intramural ureter in PUV patients [15]. The three components of the valve bladder syndrome include dysfunctional renal units, dilated refluxing ureters, and the chronically distended bladder. Bladder dysfunction with progression through childhood and into adulthood has been found to be contributory to the worsening of renal function [8, 14, 16].

Urodynamic assessment in children treated for PUV have found bladder dysfunction in up to 75 % of the patients. Three predominant patterns found were: detrusor overactivity, poor compliance, and myogenic failure [17–19]. It is generally postulated that an increase in bladder capacity with age is responsible for the transition from detrusor overactivity to myogenic failure after puberty [19, 20]. Detrusor overactivity, poor compliance, and polyuria secondary to CRF are responsible for episodes of incontinence, which causes sleep disturbances as well negatively impacts on social functioning [13].

Management of Bladder Dysfunction

Anticholinergics play an important role in managing the symptoms of detrusor overactivity, especially in conjunction with bladder augmentation in patients with poorly compliant bladder. Anticholinergics may improve both bladder compliance and sensation. The Mitrofanoff continent catheterizable channel may be considered for these patients because of the relative ease of clean intermittent self catheterisation (CISC) in comparison to the urethral route, thereby improving patient compliance [21, 22]. Intradetrusor injections of botulinum toxin A may be considered a useful treatment modality to temporarily bridge the gap between anticholinergics and bladder augmentation.

Intestinal segments are generally used for bladder augmentation with the associated risks of hyperchloremic metabolic acidosis, bacteriuria, and malignancy. The risk of malignancy is said to be between 1.2 and 2 % [23, 24] after a 10-year period from operation to diagnosis, and hence the ureter may be considered as a substrate for augmenting the bladder in selected patients needing nephroureterectomy due to persistent infection secondary to unilateral nonfunctioning kidneys with chronic dilated ureters [25].

Detrusor myomectomy may reduce the intravesical pressure but does not increase bladder capacity and durability may be limited, both of which limit usefulness of this treatment [26]. Use of a gastric segment (gastrocystoplasty) is not recommended due to haematuria–dysuria syndrome [27].

In cases of detrusor failure, the management options include timed voiding, double voiding, and CISC to ensure the bladder is kept empty and avoid bladder stones and lower urinary tract infections, CISC can however be very painful in these patients since they often have a redundant posterior urethra which makes catheterization

technically difficult. Hence, a Mitrofanoff may be preferred [26].

Sexual Function and Fertility

Risk factors for decreased sexual function and fertility in PUV patients include CRF [28, 29], abnormal prostatic urethra [30], crypto-orchidism [31, 32], leukospermia [33], and recurrent epididymo-orchitis [34–36].

Decreased libido and sexual activity are among the adverse effects of CRF [37] with ED reported in 70 % of men with chronic kidney disease [38]. This is an important risk factor as a third of patients will progress to ESRD [8, 9].

Surgery for crypto-orchidism is seen in up to 16 % of patients and the resultant reduced testicular size and testosterone levels can cause reduced sexual function [39]. However only men with bilateral crypto-orchidism have been shown to have reduced fertility than men with unilateral crypto-orchidism [40].

Recurrent epididymo-orchitis with or without secondary leukospermia is thought to be a result of reflux to dilated ejaculatory ducts due to the increased pressure in the posterior urethra [34, 35, 41, 42].

There is conflicting evidence in the literature regarding fertility in PUV patients. Some studies have shown decreased fertility [43–45] while the largest study to date has shown no difference in fertility and ED between PUV patients and the general population [46].

Follow-Up

The ability to follow the progress of young patients as they develop is paramount in attempting to understand the long-term outcomes of treatments. The only way to achieve this is to establish good quality longitudinal care for patients as they leave pediatric practice and enter adult healthcare. Young males with treated PUV need regular follow-up with measurement of urea and electrolytes, blood pressure and USS to assess the upper tracts. Periodic urodynamic monitoring, particularly when new voiding problems (retention, UTI, stones) appear or imaging and serum Cr suggest worsening renal function, is necessary.

Health education forms an integral part of Transitional care. As young patients move on into adolescence, there is a high risk of noncompliance with treatments and health education should be included to ensure compliance with e.g. medications (anticholinergics, antibiotics), voiding strategies, intermittent self catheterization/bladder washouts, and attendance at follow-up clinics. Loss of renal function with progression through adolescence is well demonstrated and not solely explained by noncompliance of teenagers. The ItalKid study authors suggested that the possible mechanisms for this finding are: (1) imbalance between glomerular capacity and increased body mass, or (2) an effect related to the changing sex hormone environment with progression [47]. In addition, adolescence and young adulthood also represent a time of sexual growth and experimentation, and for young men with PUV, erectile dysfunction, ejaculatory issues, and fertility are of paramount concern. Timely and appropriate transfer to a suitable adult urologist becomes paramount as patients grow up to enable uninterrupted lifelong follow-up, sometimes in conjunction with other medical professionals e.g. the nephrologist. The medical consequences of a patient with such needs being lost in follow-up are potentially serious and often difficult to rectify when considerable time has elapsed since the patient was last seen.

Summary

- Posterior urethral valves represent a spectrum disorder including lung hypoplasia, renal insufficiency that includes both tubular and glomerular dysfunction, impaired ureteric contractility, undescended testes, and a poorly functioning bladder.
- PUV is most commonly diagnosed in utero, although late diagnoses in young adulthood are still seen.

- Approximately 1/3 of patients develop ESRD by young adulthood, with renal deterioration often seen during and shortly after adolescence. This observation mandates close follow up of patients with PUV throughout their lives.
- Several bladder patterns may be seen on urodynamic assessment, including myogenic failure, detrusor overactivity, and poor compliance and bladder function may change throughout life, requiring periodic reassessment, particularly when new symptoms appear or renal deterioration is found.

Sexual dysfunction, including ED, hypogonadism, ejaculatory dysfunction, recurrent epididymo-orchitis and infertility are all common.

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Part IV

Upper Tract

Renal Transplantation in Patients with Lower Urinary Tract Dysfunction

14

Christine Tran and John Rabets

Introduction

Lower urinary tract (LUT) dysfunction is a leading cause of pediatric end-stage renal disease (ESRD). It is estimated that 15–25 % of children with ESRD have associated anatomic urological abnormalities that result in LUT dysfunction [1]. These problems may persist into adulthood and also comprise an important cause of ESRD in approximately 6 % of the older population [2]. It was previously thought that renal transplantation in the setting of an abnormal LUT was unfeasible and these patients were generally considered poor candidates for transplantation [1, 3–5].

While it is well known that congenital urologic disease may adversely influence the outcome of renal transplantation, advances over the past four decades in patient evaluation and management, surgical technique, and immunosuppressive regimens have all contributed to a growing body of experience with renal transplantation in the setting of ERSD associated with urological abnormalities in both the pediatric and adult populations. Twelve years after the first successful kidney transplant between identical twins in 1954, renal transplantation was performed in patients without a functional bladder when Kelly and colleagues performed the first renal transplants into patients with ileal conduits [6]. In 1971, the first pediatric renal transplants were undertaken in children with urinary diversions [7]. Marshall and colleagues described the first augmentation cystoplasty following renal transplant in 1982 [8]. Two years later, the first pediatric renal transplant drained into an augmented bladder was performed [9]. And, finally, in 1989, the first kidney transplant drained into a continent Kock pouch was described by Heritier and colleagues [10]. Subsequently, better understanding and management of the causes of LUT dysfunction have contributed to a growing number of successful cases of renal transplantation into this patient population.

The combination of LUT dysfunction and ESRD requiring renal transplantation presents unique management challenges. Patient with ESRD due to LUT problems that remain uncorrected at the time of transplantation face significant risks of patient morbidity with higher rates of urinary tract infection (UTI), surgical complications, allograft dysfunction, and graft loss [4]. These complications may be avoided with proper preoperative assessment of bladder characteristics, initiation of appropriate medical therapy and clean intermittent catheterization (CIC), and determination of the need for surgical management with either bladder

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reconstruction or urinary diversion. Successful outcomes depend not only on the input of the urologist, nephrologist, and transplant surgeon in a multidisciplinary team but also on patient and family understanding and compliance. With appropriate risk assessment and bladder management, contemporary patients have good outcomes with graft and patient survival rates similar to that of the ESRD population without LUT dysfunction [11].

Preoperative Considerations

Goals of Treatment

LUT dysfunction remains a complex spectrum of diseases where both the disease and its severity dictate treatment strategy. At present, there remains significant controversy regarding the optimal management of this unique patient population. There are currently no established guidelines defining the criteria for reconstructive surgery, optimal reconstructive procedures, and the timing of such procedures [11, 12].

Nonetheless treatment is guided by several key principles. The main goal of care is to identify, characterize, and correct LUT abnormalities prior to renal transplantation with an aim to:

1. Provide a urinary reservoir that permits storage of an appropriate urinary volume at a low, safe pressure
2. Provide a consistent and easy method of achieving complete reservoir emptying
3. Provide a mechanism for urinary continence
4. Minimize the risk of UTI

Preoperative Assessment

All patients with ESRD and a history of LUT dysfunction should undergo a comprehensive urologic evaluation to: (1) assess the appropriateness of the bladder or its substitute for urinary tract reconstruction and, (2) determine the need to remove the native kidneys prior to or at the time of renal transplantation. A general screening involves a detailed history including a history of all prior urologic interventions and operations on the urinary tract, an elimination interview to assess bowel function (for those with neurogenic bowel), a physical examination, a urinalysis and urine culture, and a renal and bladder ultrasound. Voiding cystourethrogram (VCUG) is useful to assess for the presence of reflux, voiding function, and the state of the urethra. If there is any suspicion of bladder dysfunction based on the results of the ultrasound and VCUG, then urodynamic (UDS) evaluation is performed in order to more closely assess bladder capacity, compliance, storage pressures, emptying, and sphincter function. Other indications for UDS testing include a history of neurogenic bladder, prior severe posterior urethral valve (PUV) disease, ongoing voiding dysfunction, hydronephrosis, or recurrent UTI [13, 14]. Urodynamics are a critical element in the management algorithm for this patient population and are crucial in assessing the need for further therapy to improve bladder function. Information from UDS regarding bladder emptying and drainage also plays a crucial role in the designing strategies for the prevention of infection. These studies are often repeated as necessary to assess the impact of a change in management strategy and to further optimize bladder function.

General Considerations

Bladder Compliance and Capacity

Bladder compliance is defined as the change in volume of the bladder per change in detrusor pressure as measured between the start of bladder filling and at cystometric capacity. "Normal" compliance is variable and various definitions of impaired compliance have been used. In the seminal paper by McGuire and colleagues, storage pressures greater than 40 cm H_2O were found to be associated with deleterious upper tract effects [15]. However, this value was obtained in patients with normal kidneys located

in the native renal fossae and with normal ureteral insertions. In the transplanted kidney, which is lower in the pelvis and which is often associated with a refluxing anastomosis, this cutoff is less relevant. Nonetheless, the association between upper tract fate and reservoir storage pressures is well described in the literature and, as a general rule, prolonged storage at elevated pressures leads to upper tract deterioration. Providing a urinary reservoir that allows storage of an appropriate urinary volume at safe pressures is important in the prevention of future upper urinary tract deterioration and potential graft loss. While some patients with a history of PUVs with so-called "valve bladders" can learn to empty adequately by Valsalva, there is currently a paucity of data regarding the fate of the transplanted kidney subjected to elevated storage, and possibly reflux, pressures associated with Valsalva voiding. The initial approach to addressing the non-compliant bladder thus usually involves the use of anticholinergic medications with CIC [16]. Failure of conservative management then necessitates either bladder augmentation or urinary diversion.

Bladder capacity comprises another element of normal bladder function and contributes to both urinary storage and social continence. Bladder capacity may be assessed during urodynamic evaluation by filling the bladder until the patient experiences fullness and the urge to void. Capacity can be improved with medical therapy but may ultimately need to be expanded with surgical intervention.

Reflux

Low capacity, poorly compliant bladders that store and empty urine at high pressures contribute to an increased risk of secondary VUR which may, in turn, contribute to an increased risk of renal deterioration [17]. Additionally, a new ureteral implant from a kidney in the iliac fossa may well be subjected to a greater risk of reflux, particularly in Valsalva voiders. The presence of reflux can be directly assessed by VCUG, an important element of the urologic workup that should always be performed to assess for evidence of urinary tract dysfunction.

Infections

UTI is a frequent problem among patients with complex urologic anomalies and is a well-recognized risk factor for renal allograft loss [18, 19]. Usually, the development of UTI is related to inadequate emptying of the urinary reservoir, either due to inadequate voiding or catheterization, or retained foreign body (stone). Ensuring adequate reservoir emptying is an issue that should be addressed well ahead of transplantation to avoid adverse outcomes. Persistent, symptomatic UTIs in the face of adequate CIC is a challenging issue and may be due to an unrecognized urologic abnormality that remains to be addressed, or to chronic colonization which may often be managed with continuous antibiotic prophylaxis or with a long-term antibiotic course [20]. It is critical to ensure that all patients at risk for recurrent infections due to need for CIC and/or augmentation cystoplasty are performing mechanical irrigation of the urinary reservoir and draining the reservoir at frequent intervals.

Initial Management Strategies for Bladder Dysfunction

Treatment options for LUT dysfunction are divided into two categories: (1) conservative measures involving the use of pharmacotherapy, CIC, and/or bladder training, and (2) surgical reconstruction.

Pharmacotherapy

Anticholinergic medications are the cornerstone of therapy and are titrated with increasing doses and close monitoring for changes in catheterized volumes, urinary continence, and hydronephrosis. In patients where anticholinergic agents fall short due to lack of efficacy and/or tolerability, intradetrusor botulinum toxin-A injections should be considered. While there are no studies to date specifically regarding the use of botulinum toxin-A for bladder dysfunction in the renal transplant patient, there is increasing evidence supporting its use in the treatment of neurogenic or idiopathic detrusor overactivity and overactive bladder in both the adult and pediatric populations [21].

Clean Intermittent Catheterization

CIC may also need to be initiated to maintain safe pressures and to allow periodic bladder emptying to reduce infection risks associated with urinary stasis. The reasons for initiating CIC must be carefully emphasized with the patient, family, and other caregivers. Additionally, close support during teaching and follow-up is vital to the long-term success of this management strategy. CIC also allows the care provider a good opportunity to assess patient and/or family compliance prior to renal transplantation. Compliance with a CIC regimen can be a good predictor of outcomes posttransplant. In a retrospective review of pediatric patients with LUT dysfunction who had undergone renal transplantation at their institution, Koo and colleagues found that the only patient in their series who did not achieve long-term graft survival was a teenage boy who was noncompliant with both his immunosuppression medications and CIC regimen [1].

Bladder Cycling

There is no standardized definition for a defunctionalized bladder [2]. Some authors have defined it as a bladder that has been decompressed and not used for several years [22, 23]. Errando and colleagues define a defunctionalized bladder as one with a urine output of less than 300 mL/24 h [24]. Patients with chronically defunctionalized neurogenic bladders are becoming more rare due to closer urologic management in pediatric life, which has substantially decreased the number of individuals who are progressing to ESRD in this population. In such patients, it is impossible to predict what the potential bladder function may be without further testing. Bladder cycling is an effective method to determine the characteristics of the defunctionalized bladder and to allow the opportunity to increase bladder capacity, measure compliance, and assess the ability to perform CIC preoperatively [25]. Cycling involves a progressive regimen of catheterization with instillation of increasing volumes of fluid for a set dwell time followed by bladder drainage [26]. Cycling may be performed through either a urethral catheter or a suprapubic tube. Normal saline is instilled into the bladder beginning at 50 cm^3 per instillation and gradually increasing in 50–100 cm^3 increments until patients have the urge to void. Voiding per urethra is then allowed with either the suprapubic catheter clamped or after removal of the urethral catheter. Post-void residual is measured by unclamping the catheter or with straight catheterization per urethra. Bladder volumes are then calculated as the voided volume plus the residual volume. Cycling may be used in conjunction with anticholinergic therapy to increase bladder compliance and capacity. Urodynamics is repeated at the conclusion of the period of cycling to assess for changes in bladder function. *Patients with bladder volumes less than 100 cm^3 or elevated voiding pressures face an increased risk of complications following transplantation and should be considered for bladder augmentation in preparation for transplantation.*

Surgical Intervention for Bladder Dysfunction

Providing an adequate urinary storage reservoir and complete drainage are important considerations for a successful transplantation. Surgical intervention is considered when a patient has failed pharmacological therapy, adequate drainage, and bladder cycling. Bladder augmentation offers transplant recipients increased storage capacity at safe pressures and, when combined with CIC, provides most patients with satisfactory urinary continence.

Timing of Reconstruction

Ideally, bladder reconstruction should be performed prior to renal transplantation [12, 19, 27–30]. In many cases, renal dysfunction is directly attributable to the LUT dysfunction which clearly must be corrected prior to transplantation to prevent renal allograft loss for the same reasons that precipitated native renal demise. Additionally, prior reconstruction allows for adequate wound healing in the absence of immunosuppression. Prior literature has reported bladder augmentation or creation of a urinary conduit performed specifically in anticipation of a renal transplantation an average of 3–9 months

prior to the time of transplant [2, 12, 19, 24, 27–34]. Interestingly, Garat and colleagues also suggest that bladder augmentation should not be performed too far in advance of the time of expected renal transplantation due to the increased risks of calculi formation, infection, and mucous production in the oligo/anuric patient on dialysis [30].

While not ideal, successful bladder reconstruction has also been reported following renal transplantation [1, 4, 35, 36]. In some cases, a bladder is identified that is inappropriate for ureteroneocystotomy at the time of transplantation. In this scenario, terminal loop cutaneous ureterostomy has been described as a feasible temporizing option in anticipation of future bladder reconstruction [37]. In others, LUT dysfunction was unrecognized at the time of transplant. And, finally, in a small subset, patients with borderline bladder function identified preoperatively elected to proceed with transplantation in the hopes of not needing further surgical intervention. Advocates of this approach cite the advantage of sparing patients from reconstructive surgery and its associated complications should the posttransplant bladder regain adequate function. Obviously, a major concern with this strategy is that allograft damage may result from transplantation into a dysfunctional LUT and close urologic monitoring is an essential component of the postoperative care. Patients who eventually necessitate posttransplant bladder reconstruction generally have successful outcomes. The number of patients who have undergone posttransplantation bladder reconstruction is small. However, reports suggest that this approach poses no additional risk of complications, renal allograft function, or survival. Koo and colleagues describe bladder augmentation and creation of a Mitrofanoff stoma in two of their patients 5.7 years and 11 months following renal transplantation [1]. Patients underwent bladder reconstruction due to increasing difficult catheterization through the urethra as well as worsening bladder compliance on UDS. Outcomes were comparable to those of patients who had undergone pretransplantation bladder reconstruction. Basiri and colleagues conducted a study comparing the outcomes of individuals undergoing bladder augmentation pre- and post-transplantation [29]. Graft survival rates and number of rejection episodes were no different between the two groups.

Simultaneous surgical reconstruction and renal transplantation is a third option that subjects the patient to a single operation but this is not an optimal approach. There have been, however, a small number of cases where successful bladder reconstruction was undertaken at the time of renal transplantation. Kim and colleagues report a successful outcome of simultaneous ureterocystoplasty and living-related renal transplantation in an 11-year-old boy with ESRD due to perinatal asphyxia [38]. Jones and colleagues similarly report a successful outcome in a 21-year-old patient who underwent simultaneous ileocystoplasty and renal transplantation for ESRD related to congenital sacral myelomeningocele [39]. In both of the above cases, there were no postoperative complications and the patients had stable renal function at the time of follow-up. Finally, Luke and colleagues also report simultaneous ureterocystoplasty and renal transplantation in two patients who ultimately had graft survival but who also developed recurrent pyelonephritis associated with VUR [40].

Bladder Augmentation

In the patient with ESRD and a small, noncompliant bladder, bladder augmentation remains a safe and effective method of restoring LUT function and can be approached in a manner similar to that for any other patient [41]. Broad indications for augmentation include the inability to develop a bladder capacity greater than 75 % of the expected volume by age and elevated storage pressures greater than 30 mmHg despite maximal medical management. When possible, functional augmentation is preferable to dry augmentation to allow for the development of adequate bladder capacity prior to transplant, as well as to allow for the evaluation of bladder continence and function in the preoperative setting.

A variety of different intestinal segments have been successfully used for bladder augmentation including detubularized bowel (ileum, ileocecum, or sigmoid), stomach, and ureter [27]. Detubularized ileum is the most commonly used.

However, colonic segments have also been used with good success, with the teniae coli of the colon providing a good site for future ureteral reimplantation. The use of gastric segments has also been described and was popularized in the 1980s and 1990s. Gastrocystoplasty does hold several advantages including the absence of mucus production, avoidance of metabolic acidosis, and a possible decrease in the incidence of UTI due to the acidic environment [13]. In recent years, however, gastrocystoplasty is generally avoided due to increasing recognition of potential complications. Symptomatic hematuria–dysuria syndrome has been reported to occur in up to one-third of patients undergoing this procedure [42]. Additionally, the presence of gastric secretions into an empty bladder predisposes to mucosal erosion and may place the anuric patient at increased risk of reservoir perforation [43]. These patients must be maintained on proton pump inhibitors and undergo routine irrigation with bicarbonate solution until urine output is reestablished. In addition, gastrocystoplasty has been identified as a special group at even increased risk oncogenic potential, particularly when combined with renal transplant (see Chapter 11, Husmann).

The ureter has also been used in bladder augmentation and ureterocystoplasty is a safe alternative in a minority of patients where a dilated ureter is available [34, 44, 45]. Advantages of ureterocystoplasty include the lack of mucus production (which is associated with obstruction, urolithiasis formation, and infection), avoidance of metabolic disturbances, and avoidance of the risk of bladder neoplasia. In a report of their experience with patients with ureterocystoplasty who had undergone subsequent renal transplant, Nahas and colleagues outline several key principles in using the ureter for augmentation [34]. They emphasize the need to exclude any disorder of the LUT during the evaluation of a patient with megaureter and renal dysfunction, as removal of the dilated ureter may eliminate a potential material for future bladder augmentation. They also advised reconsideration of the practice of routine nephroureterectomy for a poorly functioning or nonfunctioning kidney when treating infants with abnormal bladders due to the aforementioned considerations. Additional considerations include maintaining the renal pelvis to maximize the size of the potential ureteral patch, and detubularization of the ureteral segment prior to incorporation to abolish contractions and increase bladder capacity. Finally, special attention must be given to ureteral vascularization. At the time of nephrectomy, the kidney must be carefully removed to preserve the distal ureteral vasculature. In cases where there is a question of adequate ureteral blood supply, it is better to use a bowel segment instead at the time of augmentation. Failure of the ureterocystoplasty necessitating repeat augmentation with a bowel segment is particularly relevant in patients who had a history of prior ureteral reimplantation where the distal blood supply had been previously compromised.

Urinary Diversion

When possible, it is preferable to reimplant a graft into the native bladder if the bladder can be maintained or augmented to create a hospitable environment for a transplanted kidney. However, if the bladder is absent or in the patient with complex LUT dysfunction, an incontinent or continent catheterizable urinary reservoir may be created prior to renal transplantation. The urologist must take care at the time of diversion to place the stoma in a location that avoids conflict with a potential transplant incision. A discussion with the patient related to his/her preferred method of urinary management should be undertaken, with express discussion that the continent reservoir provides an opportunity for greater discretion and cosmesis, but also increased responsibility for maintenance (irrigations, catheterizations) compared with ileal conduit. A continent reservoir also presents increased risk of metabolic abnormalities, particularly as the graft fails with time. These patients should be closely monitored to identify and treat acid/base and electrolyte imbalances. Finally, incontinent urinary diversion remains a good option for patients who are unable or poorly motivated to perform CIC.

Native Nephrectomy

Removal of the native kidney should be considered in patients with recurrent UTI, massive reflux, recurrent stone formation (particularly into a mucous-producing reservoir), malignant hypertension, or profound nephrotic syndrome with protein wasting [46]. Limiting the risk of UTI is of paramount concern in this patient population due to the above-described risks of graft dysfunction and loss from chronic infection. Removal of the distal ureter should be considered if there is significant reflux or obstruction to minimize infection risk. The transplant surgeon should be aware of the potential impact of this procedure on the subsequent transplant, however, as dissection of the distal ureter can cause significant adhesions in the iliac fossa. Additionally, the approach toward native nephrectomy should be carefully considered if the ureter is a potential material for bladder augmentation, continent stoma creation, or transplant-to-native ureteroureterostomy in order to not disrupt ureteral vascularization. Finally, native nephrectomy may be undertaken at the time of transplantation; however, this approach is usually avoided to minimize surgical time and complexity.

Management of the Bladder Outlet and the Mitrofanoff Principle

The decision regarding creation of a continent catherizable stoma is dictated by the ability to spontaneously empty. In patients with urologic anomalies, the native urethra may be unsuitable for CIC as anatomical abnormalities can lead to difficult and painful catheterization (particularly for exstrophy/epispadias patients and PUV patients). At the same time, compliance with CIC is critical to allograft survival and it is important to make catheterization convenient, easy, and pain-free. The Mitrofanoff principle is an important consideration in this patient subset [47]. Continent catheterizable stomas can be constructed from appendix, native ureter, or ileum (tapered or transverse retubularized) into the appropriate reservoir and can greatly facilitate reservoir emptying.

Renal Transplantation

Renal transplantation is generally performed via the standard technique with a Gibson incision and placement of the allograft into the iliac fossa.

Special consideration must be given to ureteral implantation in the patient with prior urinary tract reconstruction. The Lich–Gregoir extravesical technique for ureteral implantation into the native bladder is most commonly described in the literature. However, the ureter may also be implanted into the bowel segment used for an augment or into the ureteral patch when the bladder is not easily accessible [2]. Occasionally, an intravesical approach through the augment patch to reach the detrusor is necessitated when the bladder is otherwise difficult to mobilize due to prior surgeries. If no detrusor is available at all, the ureter may be implanted into the enteric segment. In these cases, anastomosis to a colonic or gastric segment is preferred because of the thicker bowel wall. Successful transplant-to-native ureteroureterostomy has also been reported [28, 48].

In patients with an ileal conduit, the preferred surgical approach is through a midline transperitoneal incision. Evaluation of the conduit location is then performed. If there is sufficient room for kidney transplantation inferior to the conduit, the kidney can be placed on the ipsilateral side with the renal pelvis facing cephalad. If, however, there is inadequate room for transplantation on the side of the conduit, the kidney is placed on the contralateral aspect and the ureteral anastomosis is performed from that location provided that the transplant ureter is of sufficient length for reimplantation. It is obviously imperative that the ureter is not kinked with implant into an ileal conduit and if placement into the iliac fossa generates such a situation, implantation can be done into native renal vessels or the great vessels superior to the external iliac vessels.

Both refluxing and nonrefluxing ureteral anastomoses have been used. It remains a topic of controversy whether one is associated with better outcomes than another. Recurrent UTIs are a well-recognized issue posttransplantation in this

patient population; as such, some authors prefer to perform antireflux anastomoses whenever possible in the hopes of decreasing upper urinary tract colonization and infection. Nahas and colleagues report a case of decreased pyelonephritis episodes in a patient who had undergone revision of their transplant ureteral anastomosis to a nonrefluxing ureteroneocystostomy [34]. However, some authors also report similar outcomes in terms of graft survival and risk for postoperative UTI in patients with refluxing anastomoses and those with nonrefluxing anastomoses [49].

The ESRD patient with LUT dysfunction is often surgically complex and it is imperative that the transplant surgeon be aware of all prior urologic procedures in their patient at the time of transplantation. For instance, special attention should be given to the presence of the vascular pedicle and its anastomotic orientation in the augmented patient to avoid disruption and subsequent cystoplasty necrosis. Likewise, recognizing the location and orientation of a stoma mesentery in patients with prior urinary diversion is important during transplantation.

One special mention should be made regarding vessel selection in patients with exstrophy who have good sexual function. Avoidance of the hypogastric vessels should be attempted, as there remains no cross-flow between the cavernosal arteries and therefore use of the hypogastric vessels presents an elevated risk of erectile dysfunction in these individuals.

Postoperative Considerations

Management Strategies

After transplantation, it is crucial to carefully monitor bladder function [27, 28]. Most authors suggest routine renal and bladder ultrasound every 3–6 months with imaging pre- and post-drainage to assess the upper urinary tract as well as to ensure adequate bladder drainage post-catheterization. VCUG and UDS reassessment should be obtained as needed in patients with concern for impaired renal function or urologic complications. Renal function should be closely followed. In this patient population, an elevated creatinine may be due to a variety of factors. All potential etiologies should be carefully considered and evaluated including rejection, infection, and obstruction.

Posttransplantation bladder dysfunction may manifest as graft dysfunction that is associated with infection, incontinence, reflux, bladder hypertonicity, or hydronephrosis. If untreated, severe bladder dysfunction may predispose to allograft loss [1, 4]. If there is any concern for LUT dysfunction, maximal bladder drainage should be maintained with Foley catheterization or suprapubic tube. Improvement in renal function with continuous catheterization is suggestive of inadequate bladder drainage. Long-term management of bladder dysfunction is similar to the algorithm used in the pretransplantation patient. Measures to increase compliance with anticholinergics and instituting or ensuring a regular catheterization regimen comprise the initial management steps. Botulinum toxin-A injections should be considered in cases where anticholinergic agents fall short. As with the pretransplant patient who has failed conservative therapy, bladder augmentation should be considered and has been associated with good outcome even in the posttransplant individual.

The presence of intestinal segments in the posttransplant patient is associated with the risk of urolithiasis, metabolic derangements, and malignancy [50]. It is thought that mucous production by bowel segments and urinary stasis increases the risk of stone formation in augmented bladders [51, 52]. Surprisingly, the incidence of stone formation in the augmented and transplanted population has been reported to be much lower than that of the augmented population alone, which could be due to the more frequent follow-up and aggressive urinary drainage required in these patients, or the fact that passage of stones may occur asymptomatically given that the transplanted kidney is denervated. Preventive measures against bladder urolithiasis include irrigation with saline, mucolytic agents, or urea solution.

Metabolic complications of enterocystoplasty are well-recognized [32]. Hyperchloremic acidosis

is often seen in patients with ileal or colon augments or continent reservoirs. However, it is frequently difficult to ascribe acidosis to an enterocystoplasty alone as this patient population also often has additional causes of acidosis including chronic rejection, renal insufficiency, tubular dysfunction from immunosuppression, or long-term prophylactic trimethoprim-sulfamethoxazole use. For patients wheelchair-bound with myelomeningocele, respiratory acidosis may also contribute. Treatment should be aggressively pursued to prevent the adverse effects on bone maintenance.

Finally, malignancy has been reported in patients who have undergone enterocystoplasty, especially in the face of chronic immunosuppression [53, 54] [see Chapter 11 (Husmann)].

Long-Term Outcomes

Only two studies to date suggest that patients undergoing surgical management of their LUTD have a poor outcome following renal transplantation. In contrast, the majority of studies report good outcomes for renal allograft survival in patients who had previously undergone surgical management of LUTD. However, it is critical to note that most of the evidence of graft survival in congenital neuropathic bladder comes from a pediatric population. Comparison of studies is often difficult; patients with LUTD comprise a wide spectrum of etiologies and disease severity, and studies are retrospective, often small, and employ a variety of different surgical methods to create an appropriate urinary reservoir for transplantation.

Not all children with LUT dysfunction require surgical intervention prior to renal transplantation. However, early studies from the 1980s and 1990s raised concerns regarding an increased risk of complications and/or decreased renal allograft function and survival in pediatric renal transplant patients with a history of LUT dysfunction. Warshaw and colleagues reported on 52 pediatric patients who underwent renal transplantation for obstructive uropathy, 39 of which had had a prior LUT operation of bladder defunctionalization [55]. They found that posttransplant complications occurred with increased frequency in this patient population; however, graft and patient survival were comparable to that of other transplant patients. Several other studies from this time period reported on pediatric renal transplant patients with a history of obstructive uropathy, most commonly PUV disease [56–59]. Across these series, this patient subset was found to have increased rates of posttransplant complications including UTI incidence. Reduced renal transplant function and graft survival was also found in some series [56, 57]. *Of note, key risk factors for reduced graft survival included the original disease, and, most importantly, uncorrected LUT dysfunction resulting in poor storage and emptying*. These early studies served to highlight the close relation between postoperative patient performance and graft function and survival with LUT function.

With subsequent strides in preoperative patient optimization and close postoperative management, most contemporary series in the pediatric population demonstrate no difference in rates of surgical complication, graft function, or allograft and patient survival between LUTD and non-LUTD patients. In children who necessitate surgical management of LUT dysfunction prior to renal transplantation, excellent outcomes may be achieved (Table 14.1). Contemporary series including some young adult patients undergoing renal transplantation in the setting of corrected LUT dysfunction also provide promising results (Table 14.1).

Conclusion

LUT dysfunction is attributed to a range of etiologies and may lead to devastating effects on the upper urinary tract resulting in the need for renal transplantation. Patients with concomitant ESRD and LUTD pose unique management challenges to the provider team and optimal management strategies remain controversial. In general, there is consensus that establishing a high-capacity, compliant urinary reservoir with effective drainage prior to transplantation is

Table 14.1 Outcomes in patients who have undergone surgical reconstruction of a dysfunctional lower urinary tract and renal transplantation

Authors	Year	No. pt.	Mean age (yrs)	Surgical reconstruction (no. pt.)	Median follow-up	Results	Conclusion
Broniszczak et al. [60]	2010	33	11.8	IC, BA, CR	32 months	Patient survival 100 %, graft survival 97 %. UTIs most common complication	Excellent medium-term results with renal transplantation in children with lower urinary tract dysfunction and end-stage renal failure
Djakovic et al. [61]	2009	12	9.5	IC, BA, CR	5.4 years	Patient survival 100 %, graft survival 75 % (no graft loss due to LUTD)	Reconstruction of the lower urinary tract prior to renal transplantation is a safe management strategy
Nahas et al. [28]	2008	211	13	BA, CR	75 months	Compared children with ESRD due to nonurological cause, ESRD due to urological cause but with an adequate bladder, and ESRD due to urological cause requiring preoperative surgical intervention. Similar patient survival, graft survival, and surgical complication rate across all groups	With individualized management, children with severely compromised LUT function may undergo renal transplantation
Taghizadeh et al. [62]	2007	16	7.5	BA (16)	58.4 months	Patient survival 100 %, graft survival 94, 89, and 67 % at 1, 5, 10 years	Bladder reconstruction can be safely performed prior to transplantation
Mendizabal et al. [63]	2005	15	13	BA, IC	7 years	Patient survival 100, 92, 92 % and graft survival 77, 62, and 30 % at 1, 5, and 10 years with no significant difference between LUTD and non-LUTD group	Children with severe LUT dysfunction can achieve similar results to the general population following renal transplantation
Rigamonti et al. [64]	2005	24	14	BA, IC	67.2 months	Graft survival 96, 82, and 66 % at 1, 5, and 10 years (no significant difference compared to a non-LUTD group)	Drainage of the renal allograft into an augmented bladder or urinary diversion is an appropriate management strategy in the absence of a suitable native bladder
Ali-El-Dein et al. [65]	2004	15	13.5	BA, CR	4.5 years	Patient survival 93, 85, and 85 % and graft survival 93, 86, and 34 % at 1, 5, and 10 years, no significant difference compared to non-LUTD group	Renal transplantation is feasible and provides good outcomes for children with an abnormal LUT

(continued)

Table 14.1 (continued)

Authors	Year	No. pt.	Mean age (yrs)	Surgical reconstruction (no. pt.)	Median follow-up	Results	Conclusion
Nahas et al. [34]	2004	8	18	BA	50 months	Patient survival 100 %, graft survival 100 %, UTIs most common complication	Ureterocystoplasty is a safe alternative to enterocystoplasty that provides similar benefits to the use of bowel for bladder augmentation without adding further complications or risks
Neild et al. [27]	2004	66	32	IC, BA, CR	92 months	Patient survival 86 % and graft survival 66 % at 10 years, no significant difference compared to non-LUTD group	Successful renal transplantation into the abnormal LUT is possible but requires thorough preoperative evaluation and post-transplant follow-up
Luke et al. [40]	2003	20	9.3	BA, IC	62 months	Patient survival 100 %, graft survival 83 % at 5 years with no significant difference compared to a non-LUTD group	Pediatric renal transplantation into a dysfunctional LUT yields similar outcomes to transplantation into the normal LUT
Defoor et al. [66]	2003	20	4.5	BA, CR	7.3 years	Patient survival 95 %, graft survival 82 %	Severe LUT dysfunction can be effectively managed with continent urinary reconstruction in children with ESRD
Hatch et al. [31]	2001	30	12.1	IC, BA, CR	59 months	Patient survival 100 %, graft survival 90, 78, and 60 % at 1, 5, and 10 years	Drainage of transplanted kidneys into an augmented bladder or urinary conduit is acceptable in the absence of a suitable bladder

IC ileal conduit, *BA* bladder augmentation, *CR* continent reservoir, *LUTD* lower urinary tract dysfunction

desirable to avoid the potential risks of UTI, surgical complications, allograft dysfunction, and graft loss. Preoperative assessment including cystogram and UDS is essential to the successful guidance of treatment strategies. Restoration of bladder function is initially approached using conservative measures such as medication, CIC, and bladder cycling. When hostile bladder conditions despite medical management, a wide range of surgical interventions are available to address both urinary storage and emptying. Small case series in both the young adult and pediatric populations in recent years have shown promising results for the patient with LUTD undergoing renal transplantation. However, indications regarding the most appropriate surgical intervention and the timing of these interventions remain unclear, and future studies are needed with a focus on the potential risks and benefits of each approach.

Summary

- Uncorrected LUT problems at the time of renal transplantation expose the patient to significant risks of morbidity including higher rates of UTI, surgical complications, allograft dysfunction, and graft loss.
- Complications may be avoided by appropriate preoperative assessment of bladder characteristics, initiation of appropriate medical therapy and CIC, and determination of the need for surgical management with either bladder reconstruction or urinary diversion.
- Surgical intervention for LUT dysfunction in the ESRD patient undergoing renal transplantation is considered when the patient has failed pharmacological therapy, adequate drainage, and bladder cycling. Bladder augmentation offers transplant recipients increased storage capacity at safe pressures and, when combined with CIC, provides most patients with satisfactory urinary continence. Ideally, bladder reconstruction should be performed prior to renal transplantation.
- After transplantation, it is crucial to carefully monitor bladder function. Posttransplantation bladder dysfunction may manifest as graft dysfunction that is associated with infection, incontinence, bladder hypertonicity, or hydronephrosis and, if untreated, may predispose to allograft loss.
- With appropriate preoperative evaluation and management of LUT dysfunction and close postoperative monitoring, the long-term outcomes of patients with ESRD and LUT dysfunction undergoing renal transplantation are comparable to those of the general ESRD population.

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Management of Calculi in Patients with Congenital Neuropathic Bladder

15

Robert D. Brown and Manoj Monga

Introduction

Urolithiasis is a common disease with the lifetime prevalence estimated to be between 10 and 15 % [19, 53]. Patients with congenital urologic disorders such as myelomeningocele (MMC), bladder exstrophy, and posterior urethral valves (PUV) represent a special population with regard to urolithiasis. These patients are at an increased risk of stone formation due to a variety of reasons including: bladder dysfunction, urinary tract reconstruction, urinary tract infections (UTIs), obesity, and osteodystrophy.

Improvements in the medical care of the patients with congenital urologic disorders have led to increased survival and many patients survive well into adulthood. Indeed, adult MMC patients now outnumber the pediatric MMC population [25]. The majority of research to date has been aimed at stone formation in the pediatric population [62]. However, given the growth of the adult population, we might expect an increase in the incidence of stones as these patients age.

The physiologic and anatomic differences present in patients with MMC, exstrophy and PUV necessitate special management that differs from the general population. In this chapter, the focus will be on the medical and surgical management of urolithiasis within this patient population.

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Risk of Stone Formation: Lower and Upper Tract Stones (Table 15.1)

Bladder Dysfunction

Patients with MMC, bladder exstrophy, cerebral palsy (CP), and PUV have high rates of bladder dysfunction which increases the risk of developing urolithiasis. Urine retention increases the risk of UTIs which in turn leads to development of urolithiasis, and this risk is compounded by the use of catheterization to empty the bladder which introduces bacteria to the urinary tract. Lower urinary tract reconstruction is a common occurrence as a result of bladder dysfunction, and the incorporation of gastrointestinal segments into the urinary tract and presence of foreign material such as sutures can act as nidus for infection and stone formation.

Neurogenic Bladder

Urinary stasis, elevated intravesical pressures, and UTIs have all been postulated to contribute to the development of urinary tract stones within the neurogenic bladder. Up to 90 % of patients with open MMC defects and 66 % of closed defects have abnormal bladder function on urodynamic testing [24]. Symptomatic bladder dysfunction has an estimated prevalence of 16 % in the

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Table 15.1 Risk factors for stone formation

Myelomeningocele
Urinary tract infection
Bladder dysfunction—urine retention
Lower urinary tract reconstruction
Urinary diversion
Enterocystoplasty
Chronic indwelling catheter
Immobilization
Hypercalciuria
Obesity
Acidosis of urine
Exstrophy-epispadias complex
Urinary tract infection
Bladder dysfunction—urine retention
Lower urinary tract reconstruction
Bladder neck reconstruction
Enterocystoplasty
Urinary diversion
Chronic indwelling catheter
Vesicoureteral reflux
Posterior urethral valves
Bladder dysfunction—urine retention
Lower urinary tract reconstruction

cerebral palsy population, with asymptomatic dysfunction as high as 30 % [32]. MMC patients that developed urolithiasis are less likely to be spontaneous voiders and more likely to have undergone bladder augmentation or urinary diversion [62]. No literature exists regarding the development of urolithiasis in cerebral palsy patients with bladder dysfunction.

Lower Urinary Tract Reconstruction

Lower urinary tract reconstruction is a common procedure of those with neural tube defects, exstrophy-epispadias complex, and PUV. These patients are at risk of forming stones for a variety of reasons including presence of foreign material such as absorbable staples, mucous production from intestinal segments, urinary stasis, and infection [17]. Urine retention appears to be the most important risk factor for bladder stone formation as spontaneous voiders have the lowest rate of stone formation [17, 36].

Although the rate of lower urinary tract surgery has decreased in the myelomeningocele population, 11–17 % of patients have undergone diversion or augmentation [20, 64]. However, of MMC patients that formed stones, 33–38 % had undergone urinary diversion or bladder augmentation [13, 62]. Bladder reconstruction is also associated with upper tract stones. Of patients with MMC that form upper tract stones, up to 73 % had lower urinary tract reconstruction [56].

A variety of urological procedures have been employed to manage bladder exstrophy. Ureterosigmoidostomy (USS) was once a popular method of management for exstrophy and long-term follow-up showed that up to 40 % of USS managed patients developed recurrent urolithiasis [12]. Procedures that aimed to provide continence through a bladder neck reconstruction increased the risk of stone formation, with 94 % of exstrophy patients with stones having undergone a bladder neck procedure while only 43 % of non-stone formers have undergone a bladder neck procedure. Bladder augmentation also contributes to stone risk with 46 % of augmentation cystoplasty exstrophy patients having formed stones as opposed to only 15 % of nonaugmented exstrophy bladders. Up to 90 % of urolithiasis in exstrophy patients is lower urinary tract in origin [54]. Reconstructive surgery places patients at risk of forming urinary tract stones.

Infection

Within the general population, approximately 10 % of stones are struvite stones indicating an infectious cause [27]. In contrast, up to 30 % of exstrophy patients and 39–100 % of MMC patients had struvite stones on composition analysis [13, 46, 54, 62]. Fifty-three percent of exstrophy stone formers had UTIs on presentation and having an infection significantly increases the likelihood of diagnosis of bladder stones, as well as recurrence of bladder stones [54]. In patients who have undergone augmentation enterocystoplasty, all stone formers were found to have persistent bacteriuria as opposed to 75 % of non-stone formers [36], and stone formers also have an elevated urine pH [15]. In MMC patients, 64–75 % of stone formers had a history of UTIs,

while 30–38 % of MMC patients overall had previous UTIs [13, 62]. While the presence of calculi and rates of UTIs are strongly associated, whether infections beget stones or stones beget infections (or both) has not entirely been determined. Patients with reconstructed bladder and recurrent or escalating infections should be evaluated for the presence of a stone.

Other Risk Factors

Obesity

Adult MMC patients have an obesity rate of 35–37 % which is significantly higher than reported for pediatric MMC patients [9]. Obesity is a known risk factor for stone formation with a BMI over 30 conferring a relative risk of 1.3 in men and up to 2 in women [4, 61]. Obese patients are known to excrete higher concentrations of sodium, phosphate, and uric acid; however, urine pH decreases with increasing body weight [26, 43, 52]. As such, obese patients have a higher proportion of uric acid stones [5, 10]. For obese patients with other risk factors, like nonweight-bearing status, prior terminal ileal resection, or chronic bacteriuria, uricaciduria may represent an additional risk factor.

Osteodystrophy

Hypercalciuria is a known lithogenic risk factor for the development of calcium kidney stones. Patients with spinal cord injuries develop elevated levels of urinary calcium in the first few months following injury as a result of immobilization leading to bone resorption [57]. Evidence regarding hypercalciuria in patients with myelomeningocele and cerebral palsy is limited, with studies limited to the pediatric population. Okurowska-Zawada et al. [38] demonstrated that hypercalciuria is associated with bone fractures in those with myelomeningocele. Indeed, nonambulating MMC patients have a higher level of urinary calcium excretion [44]. Shaw et al. examined osteopenia in immobilized cerebral palsy patients and found three of nine patients with hypercalciuria [51]. Immobilization is a risk factor for the development of upper tract stones in MMC patients [56]. The higher rates of immobilization in MMC and CP patients may place them at risk of developing hypercalciuria and calcium-based urolithiasis.

Kidney Transplantation and Stones

Congenital obstructive uropathy, most commonly secondary to PUV, can be a devastating condition. Between 22 and 32 % of pediatric and young adult patients with PUV will progress to end stage renal disease (ESRD) [16, 41]. Studies investigating rates of progression to ESRD in the adult population with PUV are lacking. Kamal et al. [21] found that PUV was the underlying disease in 7 % of kidney transplantations at their center. Adult transplanted kidneys have an incidence of stones anywhere from 0.4 to 1.3 %, a rate lower than the general population. The low rate of lithiasis in allograft kidneys is speculated to be a result of the high level of donor screening, eliminating stone forming kidneys from the donor pool [1, 11, 23, 59]. In the pediatric transplant population, the incidence may be slightly higher, up to 2.5 % [22, 35]. It is important to note that a transplanted kidney is denervated, so spontaneous passage may go unnoticed. This may represent an important reason why the incidence of kidney stones is lower in transplanted kidneys [11]. While the risk of stone formation within the adult population of PUV patients is not well studied, patients with a history of PUV often have dysfunctional bladders with elevated rates of bacteriuria and UTI related to retained hydronephrotic native kidneys, incomplete bladder emptying, and the need for intermittent self-catheterization (ISC).

Presentation: Lower and Upper Tract Stones

The classic presentation for obstructive upper tract stones is flank pain that radiates through the abdomen into the groin [14]. In contrast, patients with congenital urologic abnormalities have variations in anatomy that predispose to infection and alter pain patterns. Two presentations are common: insidious onset, especially in patients with upper tract stones, and recurrent UTIs [62]. Patients with impaired sensation, as with MMC,

may complain of headache, nausea, vague abdominal pain, or hemodynamic changes related to sepsis or autonomic dysreflexia. Clinicians should have a low threshold for axial imaging for patients who previously passed stones with these symptoms, particularly if UA demonstrates micro/gross hematuria, fevers are present, and/or renal function is worsened [63].

The classic presentation of lower tract stones is infection and pain/bleeding at end-micturition. Like upper tract stones, patients with MMC have impaired sensation and may not report symptoms. Diagnosis can be by axial imaging or cystoscopy. Cystoscopy can prove challenging in a capacious reservoir or augment with multiple folds and small stones may well be missed in this scenario.

Medical Management

Evaluation of urolithiasis in the adult patient with congenital urologic abnormalities should begin with a thorough history. Complete history of prior stone episodes should be obtained. A history of lower urinary tract reconstruction can indicate a risk of infection, urine retention and stones, and any gastrointestinal surgeries may indicate altered dietary absorption patterns. If the patient performs ISC, they should be asked about the frequency of catheterization and use of any irrigation. Recent urine cultures should be reviewed to determine if protease-forming bacteria are present and/or if the same bacteria keeps representing. Both of these factors suggest a stone is present. Previous urodynamic studies may point to urine retention, a risk of both infection and stone formation.

Laboratory Evaluation

Initial evaluation of the stone formers should include some basic laboratory tests. Stone analysis, if available, can allow for targeted medical management. Imaging for current or residual stone should be done. Non-contrast CT scan can be used for diagnosis and evaluation of any anatomic abnormalities. Initial serum tests should include serum calcium and uric acid as well as urinalysis with pH and urine culture, all of which can give an indication to underlying metabolic reasons behind stone formation.

Comprehensive metabolic evaluation including 24 h urine chemistry should be considered in all patients with recurrent urolithiasis. In a study comparing stone formers to non-stone formers having undergone enterocystoplasty, stone formers were more likely to have elevated urinary calcium and pH and decreased urinary citrate and volume [15]. Hypercalciuria may also be seen as a result of osteodystrophy in patients that are nonambulatory such as those with cerebral palsy and MMC [38, 44].

Diet

No studies have been done examining diets in adult patients with congenital urologic disorders. The distribution of stone composition varies from the general population and thus, dietary recommendations may differ from the general population. These patients have a high rate of both calcium phosphate and struvite stone formation and this should be considered when giving any empiric dietary recommendations [13, 46, 54, 62]. However, metabolic evaluation including 24 h urine chemistry and stone composition remains the standard for guiding individualized dietary recommendations.

Importantly, patients with neurogenic bladder from MMC likely also have slow bowel transit and if they have previously had terminal ileal resection or resection of a large segment of their absorptive bowel, may have malabsorption.

Medications

Medications to be used will be based on laboratory evaluation including 24-h urine electrolytes and stone composition. Recurrent UTIs are an important risk factor for recurrent stone formation within this patient population, and prophylactic antibiotics might be considered for prevention of stones [54, 62]. However, some recommend against this as a strategy as it increases the risk of

developing drug-resistant organisms [40]. One study found a relationship between methane, small intestinal bacterial overgrowth, and recurrent UTIs in MMC patients. Intestinal decontamination with antimicrobials may play a role in preventing recurrent UTIs [37]. Currently, no studies have focused on the role of antibiotic prophylaxis in stone prevention in these patients.

Elevated urinary calcium can be a risk factor within this population. Patients that had bladder augmentations and form stones have higher levels of urine calcium [15]. Spina bifida and cerebral palsy patients that are immobilized and form stones often have elevated urinary calcium [44, 51]. Hydrochlorothiazide was studied as a method to prevent osteodystrophy in immobilized MMC patients. The study suggested that hydrochlorothiazide did not improve bone mineral density but was shown to decrease urinary calcium levels [45]. How effective hydrochlorothiazide is at reducing stone formation within immobile patients remains to be studied.

Adult MMC patients have a high obesity rate putting them at risk of uric acid stones. Uric acid stone formers often have urine chemistries showing normal uric acid but low urine pH [49]. For a stone >4 mm, a hounsfield unit density of ≤500 on computed tomography and a urine pH ≤5.5 has a positive predictive value of 90 % for uric acid composition [55]. Allopurinol can be considered to further decrease the urine uric acid concentration. However, the more important risk factor is urine pH which decreases the solubility of uric acid [5, 26, 43, 52]. Potassium citrate or bicarbonate can be considered in these patients to increase the urine pH. This treatment may be especially effective in MMC patients who already have metabolic acidosis from chronic renal insufficiency and/or respiratory acidosis from the myriad of pulmonary conditions to which they are prone, although efficacy remains to be determined in well-designed studies.

Bladder Management

Spontaneous voiding is the optimal bladder management for preventing the formation of stones [62]. However, in those with bladder dysfunction, methods to reduce urine retention should be employed. Currently, ISC is considered the gold standard for management of the neurogenic bladder [58]. No randomized controlled studies have been done comparing ISC and chronic indwelling catheters [18]. In retrospective studies, chronic indwelling catheters increase the risk of bladder stone formation [3, 31, 39].

One method shown to potentially reduce the risk of stone formation in augmented bladders is the use of bladder irrigation. Patients having undergone bladder augmentation were instructed to wash twice weekly with 240 mL of saline and once weekly with a gentamicin sulfate solution (240–480 mg/L) at a volume of 120–240 mL. Only 7 % of patients undergoing this protocol formed stones as opposed to 43 % undergoing standard ISC. However, compliance with bladder irrigation may prove difficult, particularly among adolescent and young adult patients [17].

Surgical Management

Contractures, obesity, body habitus, and prior bladder augmentation or urinary diversion all add a degree of difficulty to procedural management of stones in patients with congenital urologic disorders. Contemporary studies of surgical stone treatment in MMC, CP, exstrophy, and PUV patients are limited. Almost all studies group all spinal cord dysfunction together when examining outcome and complications. Body habitus, respiratory status, stone size, and density should be considered when choosing an appropriate procedure for stone removal. Due to abnormal body habitus, many of these patients are high-risk anesthesia patients. Restrictive airway disease due to obesity, scoliosis, and weak abdominal and thoracic musculature (all of which are common among MMC patients) can make general anesthesia and patient positioning very difficult. Further, gaining percutaneous or ureteral access may be difficult or not feasible. Most patients will require multiple procedures to obtain stone-free status. It is advisable to place the patient in lithotomy position in the clinic to ascertain whether the lower extremities can be

placed in lithotomy position to provide enough room for retrograde endoscopic management prior to deciding which approach to utilize for upper tract stones.

Upper Tract Management

Extracorporeal Shockwave Lithotripsy

The use of extracorporeal shockwave lithotripsy (ESWL) for treating upper tract stones has seen limited study in patients with MMC, CP, exstrophy and PUV. Only retrospective studies looking at the utility of ESWL in patients with spinal cord dysfunction have been done (Table 15.2). The success rate of ESWL within these studies is between 50 and 70 %. However, there is a high rate of ancillary procedures performed and the time to stone clearance is considerably longer than in the general population [6, 34]. Ramsey and McIlhenny [47] suggested that ESWL could be considered as part of a multimodality treatment strategy for patients with spinal cord dysfunction. If complete clearance is not achieved, the residual stone may act as a nidus for infection stone formation especially in those with recurrent UTIs. ESWL is particularly advantageous as it can be done without anesthesia [47]. ESWL should be considered in all patients with smaller stones and high-risk anesthesia patients.

Ureteroscopy

No contemporary studies have been performed on ureteroscopy in patients with MMC, exstrophy, or PUV. Patients with neurologic dysfunction present challenges for ureteroscopy as they often have abnormal body habitus, contractures, and prior lower urinary tract surgeries such as augmentation or diversion that make gaining retrograde ureteral access very difficult [47]. However, ureteroscopy may still be a viable treatment with careful patient selection. In patients with ureteral stones in which retrograde ureteroscopy is not feasible, antegrade ureteroscopy with percutaneous access should be performed [47].

Percutaneous Nephrolithotomy

Percutaneous nephrolithotomy (PCNL) is the standard treatment for stones over 2 cm in diameter [47]. However, many patients with MMC and cerebral palsy have musculoskeletal deformities including scoliosis that can make PCNL challenging [2]. Musculoskeletal deformities not only alter anatomy to make gaining percutaneous access difficult, it can impair respiratory function making ventilation difficult [42]. In retrospective studies looking at PCNL stone-free rates (Table 15.3) in patients with spinal cord dysfunction, only 47–60 % are stone free following one procedure [2, 33, 48, 60]. The majority require multiple procedures including 2–3 PCNLs or multiple ESWLs to render the patients stone free. The rate of major complications is much higher than the general population. Between 8 and 18 % of patients with spinal cord dysfunction have major complications including death, sepsis, seizures, and pneumothorax, in part due to the fact that impaired sensorium in the abdomen and autonomic dysreflexia may limit or confuse a provider to making a prompt diagnosis

Table 15.2 Shockwave lithotripsy in myelomeningocele

Author	Patients	Age	Retreatments	Hospital stay (days)	Stone free	Time to stone free (months)	Complications
Niedrach	11 (4 with spina bifida)	23.75	3 of 4	2–18	1 of 4	8	3 Intraoperative (hypertension, hypotension, bradycardia), 2 postoperative (Fever >38.5 °C)
Delivelioti	15 (5 with spina bifida)	18–57	8 of 15	0–7	10 of 15	6–20	2 Intraoperative (bradycardia), 5 postoperative (2 sepsis requiring ICU, 3 fevers >38.5 °C)

Table 15.3 Percutaneous nephrolithotomy in myelomeningocele

Author	Patients	Age	Complications	Stone free after 1 PCNL	Recurrence rate
Symons	10	28.4	6 (1 death due to arrhythmia, 3 postoperative fevers, postoperative hypotension)	47 %	10 %
Rubenstein	23 (9 with spina bifida)	11 to 60	3 intraoperative, 16 postoperative (11 fevers >38.5 °C, 2 hydrothorax, transfusion, ileus, DVT, retroperitoneal abscess)	NR	43 %
Alsinnawi	5	28	4 (2 transfusions, 2 fevers >38.5)	60 %	80 %
Nabbout	21 (7 with spina bifida)	38.8	11 (3 urosepsis, 6 transfusions, 1 pneumothorax, 1 perforation)	54 %	NR

NR not recorded

of these conditions. Median-reported hospital admission times are between 7 and 13 days [2, 33, 48, 60]. In select cases, supine positioning and epidural anesthesia can be considered to improve respiratory function and percutaneous access [28]. In patients with musculoskeletal deformities, CT-guided percutaneous access may offer better outcomes [29]. PCNL should be considered the treatment of choice for any large kidney stone in patients with MMC, CP or exstrophy, but as these are complex patients, they will often require multiple procedures, have more complications, and require long hospital stays.

Lower Tract Stones

Within the general population, 5 % of urolithiasis is lower urinary tract in origin [50]. In contrast, 50 % of stones are lower tract in MMC patients and up to 90 % in exstrophy patients, and many of these stones form within a reconstructed lower urinary tract [54, 62]. First line treatment of bladder stones consists of an endoscopic or percutaneous approach [30]. Indeed, a comparison of percutaneous removal of bladder stones to open cystolithotomy in augmented bladders has shown that those undergoing a percutaneous approach have less postoperative pain, shorter hospital admissions, and decreased morbidity [8]. Patients with neurogenic bladder treated through the percutaneous approach have a high stone-free rate and low complication rate [7]. A percutaneous approach should be considered in all patients with bladder stones.

Conclusion

Adults effected with myelomeningocele, bladder exstrophy, and PUV who develop urolithiasis can present a challenge to treat. Bladder dysfunction, urinary tract reconstruction, non-ambulatory status, and recurrent infections place them at risk of developing stones. Anatomic and physiologic differences can alter both medical and surgical treatment of stone disease within this population.

Summary

Factors that contribute to the development of urolithiasis in patients with congenital neuropathic or reconstructed bladders include:

- Bladder dysfunction
- –Recurrent UTI
- Prior lower urinary tract reconstruction
- Osteodystrophy secondary to immobilization

Presentation may include recurrent/escalating UTIs or new incontinence and clinicians should have a low threshold for axial imaging in patients with risk factors.

Laboratory evaluation in the acute setting includes: urinalysis, urine culture, and urine pH.

(continued)

(continued)

The gold standard for metabolic evaluation includes 24 h urine chemistry and stone composition, although urine pH, serum calcium, and uric acid may also help with diagnosis.

Bladder irrigation with or without antibiotic solution should be encouraged in recurrent bladder stone formers. Surgical treatment will likely be multimodal with patients often requiring more than one procedure for stone clearance.

Surgical planning should include consideration of:

- Prior surgical interventions/ reconstructions
- Body habitus (obesity, lower extremity contractures)
- Respiratory status
- Stone size and density

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Vesicoureteral Reflux and the Adult

16

Ariella A. Friedman and Moneer K. Hanna

Introduction

Vesicoureteral reflux (VUR) refers to the retrograde flow of urine from the bladder to the kidney. It occurs in 1–2 % of the population [1–3] and in 30–40 % of children undergoing imaging evaluation for urinary tract infection (UTI) [4–7]. VUR is three times more common in white than in black children, is twice as common in girls, and decreases in incidence with age [8]. In the first year of life, rates of VUR are similar in both sexes, whereas there is a 4:1 ratio of girls to boys with VUR among preschool and school-aged children [9–12]. VUR may be classified as primary or secondary. Primary VUR, which is more common, occurs in the absence of any additional pathology, while secondary VUR may occur as a result of lower urinary tract obstruction, neurogenic bladder, or following surgical procedures, such as renal transplant or ileal conduit creation. VUR is graded according to the International Classification System of VUR, ranging in severity from grade I (mild) to grade V (severe) [13]. It is associated with an increased risk of UTI and renal scarring [14], which may lead to chronic kidney disease (CKD), hypertension, and end-stage renal disease (ESRD) in the most severe scenario [15–17]. Most cases of primary VUR are successfully managed in childhood, and so adult urologists encounter it relatively infrequently.

However, there are several aspects to consider in the long-term effects of VUR in adulthood:

- The pathophysiology of renal scarring in VUR is debated. While VUR, UTI, and renal scar are certainly linked, a portion of patients with VUR have congenital renal dysplasia. This has implications for the expectations of normalcy in the adult kidney of a patient with congenital VUR.
- VUR is a known risk factor for certain morbidities in adulthood, including hypertension, etc. All patients with a history of VUR should be counseled to be vigilant for these sequelae. In turn, practitioners should be well-aware of these sequelae in order to provide proper patient care and follow-up, even beyond the stage of "definitive" treatment.
- The disease process in VUR varies with patient age, degree of reflux, presence of associated conditions, the morbidity of the process within a given patient, as well as other biologic and social aspects. All of these factors may impact the likelihood of spontaneous resolution and yield a variety of treatment options, all of which have their associated consequences later in life.

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- Even when corrected, certain patients are at risk for noteworthy sequelae of VUR.
- VUR is heritable, which makes family counseling an important aspect of patient management.
- Finally, VUR may remain undetected until adulthood and serve as an unrecognized source of patient morbidity. Alternatively, de novo VUR may manifest in adulthood, with symptoms only beginning then. This is particularly true for secondary VUR that arises as a congenital neuropathic bladder matures.

The literature on VUR is vast and often conflicting. Additionally, the clinical course of VUR varies widely, from complete resolution to persistence, and with no morbidity to ESRD, with limited ability to predict clinical course. This chapter aims to address all of the above points, based on the best available evidence.

The Nature of Renal Dysplasia in VUR

The mechanism of primary VUR is believed due to a large diameter of the ureter relative to its course within the bladder wall [18]. This may be due to an abnormally lateral ectopic ureteral orifice [19], although not in all cases [20]. As a result, the ureteric lumen does not coapt with rising detrusor filling and emptying pressures. In turn, retrograde urine flow ensues [21]. Urinary tract bacterial colonization and ascent associated with VUR [22, 23] enable renal parenchymal invasion and pyelonephritis [24, 25]. Bacterial infection may cause endothelial and microvascular damage, as well as a host immune response [14, 26, 27]. This response consists of an inflammatory reaction that yields tubulointerstitial damage, collagen deposition, and corticomedullary fibrosis; this fibrosis is associated with calyceal deformity and parenchymal thinning and is commonly labeled as renal scar [28–30]. Scar formation may, in turn, predispose to UTI. This may be due to problems with impaired local perfusion [28]. In addition, renal scarring is believed to put patients at risk for hypertension, ESRD, and pregnancy-related complications [31–40].

Most evidence suggests that renal scarring in VUR likely develops over time and relates to increased episodes of pyelonephritis. VUR is a known risk factor for pyelonephritis in both adults and children. Additionally, others have identified prompt recognition of febrile UTI and prompt initiation of antibiotic therapy (especially within the first 24–48 h) as the most important factor in preventing new scar formation [30, 41–48]; this lends support to the theory that reflux of infected urine is the primary contributor to new scar formation.

However, patients may demonstrate a history of acute pyelonephritis and renal scar development but failure to demonstrate VUR on VCUG [49]. In one study, Rushton et al. [50] found rates of new scar development equal in those with and without VUR. Thus, evidence might seem to suggest that VUR is not always necessary for scar formation. It should be noted, though, that these patients might only demonstrate VUR in the setting of an active infection and may represent a cohort of patients who have what is known as occult VUR [51].

Additionally, some patients with VUR have been found to develop renal scarring despite no documented prior UTIs [52–54]. This is especially true in patients found to have VUR and scarring shortly after birth [55–59]. Stock et al. [60] analyzed 19 patients with unilateral grade IV and V VUR, who were placed on antibiotic prophylaxis at birth and underwent ^{99m}technetium glucoheptonate radionuclide renal scan at 4–6 weeks, prior to the development of any UTI. They detected abnormal split renal function, renal size, or isotope uptake in all patients. In three patients that ultimately underwent nephrectomy, pathology revealed severe renal dysplasia in all, consisting of primitive ducts and metanephric cartilage rests. With the high utilization of prenatal ultrasound, some have detected renal damage in up to 30 % of patients with VUR prior to any UTI [53, 61–63]. Though one systematic review found the incidence of preexisting scars prior to UTI low at 0.6 % [64], sampling bias of more mild cases may have made this a low estimate, and the true incidence may be higher. More so, in many, renal scars are present when reflux is discovered at the initial evaluation of UTI [56, 65].

Further, infection alone is not the only mechanism for acquired scar formation. Early studies recognized that sterile reflux yields renal scars in the presence of high bladder and renal pressures [14, 25, 66–69]. This may be particularly true with dilating VUR (i.e., grades III–V), which is postulated to result in mechanical injury akin to a "water hammer" effect [70]. This high pressure is believed to lead to intrarenal reflux of urine into the renal parenchyma, which may contribute to renal injury. The degree of VUR is certainly a risk factor for scar formation: those with high-grade VUR are 2–6 times more likely to have scarring compared to those with low-grade VUR and 8–10 times more likely than those without VUR at all [64, 71].

Finally, many children with VUR—even with episodes of UTI—do not develop renal scars [7]. Only 15 % of children with an initial febrile UTI, for example, will develop a renal scar that persists beyond the acute infection [64]. The RIVUR trial found an even lower rate of scar formation: the authors reported a 15 % rate of acute cortical defects and a 4 % rate of persistent scar on ^{99m}Tc dimercaptosuccinic acid (DMSA) scan after initial UTI [7]. However, this lower rate may be due to the fact that the majority of children in this study had relatively low grades of VUR (i.e., grade II and III). ACE genotype polymorphisms may play an important role in individual patient propensity for scar formation [72–74]. However, this relationship may not persist on multivariable analysis [75].

Thus, there is what appears to be a wide variety in the etiology of renal scar formation. Scar may occur as a result of reflux of infected urine [67], it can occur due to sterile reflux alone [26], or it may relate to a congenitally dysplastic kidney, a priori the ill effects of VUR [76–79]. Despite a variety in their presentations and demographics, certain patient cohorts are known to more commonly develop renal damage and morbidity, such as male infants found to have severe bilateral VUR and older girls of roughly toilet training age with more mild VUR and a history of UTI [80]. In the former, scarring is probably congenital and is more accurately termed renal dysplasia [81], whereas in the latter, scarring may be acquired. The implications of renal scar etiology are important in determining to what extent renal impairment is preventable and by what means to best achieve this protection. However, the process is not so distinct, and overlap is likely [70]. It has been proposed that the congenital dysplasia associated with VUR and the scarring that results from febrile UTIs and VUR are each separate phenomenon that may coexist or occur in isolation [76]. Alternatively, the complex embryologic interaction between the mesonephric duct and metanephric blastema may predispose to both VUR and dysplastic renal development during aberrant organogenesis [76, 82]. This interplay makes studying the phenomenon of renal scarring and reflux nephropathy a challenge.

Who Is Most at Risk for Acquired Scar Formation?

While the mechanisms for scar formation are varied, most agree that the greatest risk for scar formation is in the young. The incidence of acquired scars is highest in younger children, with a 23.7 % incidence of new scars in children under 2 years old, a 9.8 % incidence in those 2–4 years, and a 4.6 % incidence in children over 5 years old [83, 84]. Pylkkanen et al. [85] noted that those younger than 1 year old were at greatest risk for scar formation and that at puberty, new scar formation ceases. Others further substantiate that young children are the most susceptible to scar formation following infection [86–88]. In contrast, it appears that the likelihood of new scar formation is lower in adolescence and adulthood [44, 67, 89]. Scar formation is also more likely to result in patients with secondary VUR vs. primary VUR [90]. Additionally, some have implicated certain genotypes, i.e., ACE polymorphisms, as a risk factor for scar development, with a near fivefold increase in those with the most susceptible polymorphisms [73, 75, 91]. It is unclear whether the severity of VUR affects the likelihood of scarring: one study found an 18-fold increase in scar formation among those with higher grade reflux [92], although others have not

demonstrated an association between VUR grade and scar formation [93].

While infants and children are most susceptible to developing scars, due to the tendency of UTIs to recur along with their incident risk of scar, as well as the irreversible nature of scars once acquired, the prevalence of renal scar tends to rise over time. When followed into adulthood, 49–58 % of patients with a history of childhood VUR have renal scars [94–96]: 35 % with unilateral scarring and 24 % with bilateral scaring. While these numbers seem high, it is noteworthy that with present aggressive management of VUR, to be described in later sections, rates of adult scarring in today's children may one day prove to be lower, but this remains to be seen.

The Pathophysiology and Long-Term Outcomes of Reflux Nephropathy (Table 16.1)

Acquired renal scarring may represent the immediate result of an acute pyelonephritic episode. However, the broader and more encompassing term for the overall renal morbidity due to VUR and its downstream effects is reflux nephropathy [10]. Reflux nephropathy manifests as focal parenchymal scar formation, a more generalized impairment of renal function, and impaired renal growth. Reflux nephropathy serves as the underlying cause of a host of related problems, such as proteinuria, CKD, hypertension, and ESRD. It is significantly correlated with degree of VUR [69, 97–99]. Renal tubular acidosis may also develop and might be an etiology of impaired somatic growth of the child [100, 101]. As a result, the general aims of managing VUR are to minimize renal morbidity.

Table 16.1 Sequelae of VUR

Febrile UTI
Reflux nephropathy
Renal scar
Impaired renal growth
Proteinuria
Chronic kidney disease
End-stage renal disease
Systemic effects of reflux nephropathy
Hypertension
Renal tubular acidosis
Impaired somatic growth
Pregnancy-associated complications

Impaired Renal Growth

In addition to focal scar formation, VUR may affect overall renal growth. Kidneys with a history of VUR are 12 % smaller than those without VUR, and those with dilating VUR are, on average, 16 % smaller than those associated with non-dilating VUR [102]. Hypoplasia may exist even in the absence of scar formation [103]. Thus, renal size should be noted and followed in patients with VUR. This hypoplasia is associated with reduced GFR but generally has not been found to increase risk for hypertension or proteinuria [102, 104]. There is debate as to whether segmental hypoplasia (i.e., the Ask-Upmark kidney) is associated with hypertension [102]; certainly, the association has been reported [105].

Chronic Kidney Disease

One of the most notable morbidities of VUR relates to the development of CKD. CKD has been known to develop in 3–11.4 % of patients with VUR and on long-term follow-up may be as high as 18 % by 15 years [96, 106, 107]. VUR is the third most common cause of CKD in children [106]. Some have found a serum creatinine >0.6 mg/dL to be the most important predictive factor for progression to CKD [108]. Older age at diagnosis is also a strong risk factor development of CKD, which has important implications for those diagnosed later in life. Bilateral high-grade VUR is also a risk factor: in those with bilateral high-grade VUR, prevalence of CKD can be higher at 15–54 %, compared with 11 % for those with unilateral VUR [107, 108]. Additional risk factors for the development of CKD in VUR include hypertension, grade V VUR, proteinuria, bilateral renal damage, and prolonged delay from

time of UTI to diagnosis. Of note, those with prenatally detected VUR are no more likely than those detected after febrile UTI to have chronic renal insufficiency [108].

The presence of scar is crucial in the progression to CKD. In the setting of bilateral renal scars, one study with three decades of follow-up found CKD prevalence at 83 %, with 19 % of those as moderate to severe. In contrast, 68 % with unilateral and 58 % with no scars had CKD, all cases mild [96]. While CKD in this study was found among patients without renal scarring, many series have found that those without scars do not develop CKD [107, 109]. It is thought that with parenchymal loss from scarring, hyperfiltration in remnant glomeruli causes glomerulosclerosis, activation of the renin–angiotensin system, and progressive renal deterioration [110, 111]. Puberty and the demands of increased growth may be a turning point for this development. Elevated urinary α1-microglobulin may serve as an early harbinger for this deterioration [112], with the development of proteinuria representing more advanced renal deterioration and poor prognosis [16, 113–116]. Previous studies identified a significant risk of developing CKD in long-term follow-up of patients with VUR [40, 117]; in recent years, though, the likelihood of developing CKD due to VUR has improved from 11 to 2 % [107].

End-Stage Renal Disease

Historically, in older series, VUR was the etiology of ESRD in up to 25–50 % of pediatric cases [118–121], representing the most common cause of ESRD in children. Similarly, VUR was a cause of ESRD in 5–16 % of adults with renal failure [17, 40, 117, 120, 122–126]. Today, however, due to successful strategies at detection and management, patients with a history of VUR represent only 5 % of the pediatric ESRD population [127]. VUR is a much less common etiology in pediatric patients undergoing dialysis (3.5 %) [128] and those receiving renal transplants (5.2 %) [129]. Of note, these numbers only relate to primary VUR; VUR in conjunction with other underlying urologic etiologies are listed separately in this registry. Likewise, the proportion of adults with ESRD with VUR as a cause is much lower at 0.22 % [130].

Based on this discrepancy between the high prevalence of VUR and the low prevalence of VUR as an underlying diagnosis in pediatric ESRD, relatively few cases of VUR progress to ESRD: it can be extrapolated that VUR leads to ESRD in roughly 0.7–13.4 per million patients, depending on one's estimate of VUR in the general population [127, 131–133]. Risk factors for progression include older patients, as well as patients with bilateral disease, bilateral grade V disease, a more advanced CKD stage, renal scarring, proteinuria, hypertension, and a history of UTI [54, 121, 134]. One study with one of the longest follow-up periods (37 years) assessed the development of ESRD in a Finnish population with VUR and found a strong risk for development in patients with renal scarring and renal impairment [96]. In this study, 7 % progressed to ESRD: 4.5 % had died due to renal disease, 2.6 % had undergone transplant, and 0.3 % were on dialysis. On ultrasound, 34 % had unilateral scarring, 24 % had bilateral scarring, and 67 % had evidence of renal impairment. Finally, VUR also predisposes to early progression of ESRD in children with other genitourinary anomalies, i.e., solitary kidney, bilateral hypoplasia, and posterior urethral valves [135].

Systemic Effects of Reflux Nephropathy and Their Long-Term Outcomes

Reflux nephropathy is postulated to exert systemic morbidity as well, secondary to the renal injury it causes.

Hypertension

Hypertension in reflux nephropathy is primarily believed to be secondary to the development of scar. Scar formation reflects renal fibrosis that, in turn, leads to local ischemia [136]. This prompts the release of renin, causing activation of the

renin–angiotensin–aldosterone system and the development of hypertension [137–141]. In more advanced cases of reflux nephropathy, more generalized renal damage may also play a role in hypertension development [142]. Once present, hypertension can contribute to further deterioration of renal function and exacerbation of CKD [32, 107, 143–145].

Reflux nephropathy is a relatively common cause of hypertension in childhood. Historically, scarring served as the cause of pediatric hypertension in 14–50 % [146–148]. More recently, it has been reported as the cause in 20–40 % [149–152]. Hypertension develops relatively early in patients with VUR, usually between 15 and 30 years old [153].

On long-term follow-up into adulthood, many studies also note a substantial incidence of hypertension, ranging from a 4.2 to 38 % incidence on 1–19 year follow-up [15, 32, 95, 107, 138, 153–158]. One study found a 52.6 % rate at 17 years follow-up [159]. Yet another study identified hypertension in 3 % at follow-up overall, with a 2, 6, and 15 % estimated incidence at 10, 15, and 25 years of age and a final rate of ≥35 % in those 20 and older [160], although nearly half of the patients in this study had renal damage at presentation. Part of the reason for such widely varying estimates may be due to inconsistent definitions of hypertension, variations in blood pressure monitoring, incomplete recording of reflux grade, and differing rates of surgical correction in these studies [161].

The development of hypertension in the setting of VUR is dependent on a variety of factors, including the degree of parenchymal damage (especially scar formation), unilaterality or bilaterality, the degree of CKD, rates of UTI, and patient age [152, 160]. Hypertension affects at least 10 % of patients with renal scarring (anywhere between 20 and 45 % with bilateral scars and 11 % with unilateral scars) [162] and affects 33.9 % with severe renal scarring [158]. Beetz et al. [155] found an 11.5 % rate of hypertension on 11 years follow-up in those with scars vs. a 2.3 % incidence in those without scars. Wolfish et al. [163] also found over 10-year follow-up that those without renal lesions did not develop hypertension. Smellie et al. [95] found on long-term follow-up that of the 7.5 % of patients that developed hypertension, renal scarring was present in 88 %. Hansson et al. [164] studied adult females with a history of childhood UTI and noted that at an average of 23 years follow-up, hypertension was more likely in those that had developed scars. Thus, in patients with hypertension due to VUR, renal scar is almost always present and serves as a major risk factor for its development. Overall, an estimated 15–20 % of children with renal scarring develop hypertension [165]. In adulthood, that number rises to 30–40 % among patients with long-standing reflux nephropathy [152]. In contrast, the rate of hypertension in the healthy adult population (age 35–74 years old) is 28 % [166].

Hypertension may also develop in patients with a history of VUR, even after surgical correction; one study found a prevalence of 29 % in adults that had been treated in childhood for VUR, with diastolic blood pressure most affected [96]. The presence of CKD is also a major risk factor for developing hypertension: one study found a 52 % risk of developing hypertension by adulthood in those with CKD, compared with 1.4 % without [107].

ACE inhibitors have been shown to slow the progression of renal deterioration and proteinuria in reflux nephropathy [109, 167] and are an ideal first-line agent in managing VUR-associated hypertension.

Impaired Somatic Growth

Additional extra-renal manifestations of reflux nephropathy may include impaired somatic growth. Impaired somatic growth is a known consequence of CKD, and certainly patients with CKD due to VUR are similarly at risk. However, it is unclear if CKD is a necessary prerequisite for impaired somatic growth or if impaired growth may occur due to other VUR-related mechanisms, even with normal glomerular filtration rates. Distal tubular damage may occur even before scar formation, impairing both concentrating and acidification

capabilities of the nephron [168]; however, this damage becomes most severe when renal scars and hypoplasia develop [169]. Somatic height and weight have been found to be most impaired compared with age-matched controls when bilateral renal lesions are present [101]. However, catch-up growth to normal may be noted following puberty [170].

Limitations of the Available Literature in Characterizing the Effects of Reflux Nephropathy in Adulthood

Studies on the long-term follow-up of patients with VUR are imperfect in several ways. Firstly, for some of the earliest studied patients, follow-up may be as long as 40 years, and more modern treatment paradigms, including concomitant management of voiding dysfunction, may yield different outcomes than those achieved by the medicine practiced decades ago. Additionally, those detected decades ago, before the era of prenatal ultrasound and sibling screening, may represent a selection bias towards those with higher degrees of symptomatic UTI, renal scarring and reflux nephropathy. Further, many studies from decades prior utilized IVP for scar detection, rather than the more sensitive nuclear medicine tests that are available today. With nuclear medicine tests replacing IVP for this indication, subtler scarring is detectable presently, and older studies generally represent a cohort with more advanced disease [54]. Thus, long-term outcomes of patients with VUR should be understood within the context of these historical differences. Outcomes may presumably be improved for today's cohort of VUR patients, but only time will tell.

Secondly, many older studies are fraught with methodological limitations. These include inconsistent or incomplete VUR grade reporting, vague inclusion criteria for UTI, lack of distinction between febrile and afebrile UTI, and varied methods of detecting renal lesions (i.e., IVP, US, or DMSA). Further, most of the older (and even current) studies on outcomes in reflux nephropathy are retrospective and have a wide range of patient selection criteria, and few have long-term follow-up into adulthood.

Thirdly, reflux nephropathy may develop due to a multitude of etiologies as discussed, including congenital renal dysplasia, acquired pyelonephritic scar, and high-pressure sterile reflux. In some, a single cause may be at play, whereas in others, a pathologic continuum may exist. Clinically, these etiologies are often difficult to tease out, and academically, most studies are not designed to make this distinction. As a result, there is limited ability to quantify the acquired, ongoing effects of VUR on reflux nephropathy vs. those that are congenital and immutable.

Despite these limitations, certain patterns commonly emerge that may be helpful in providing management recommendations. The regular assessment of overall renal function, split renal function, blood pressure, and somatic growth in patients with VUR is imperative. Assessment of creatinine level may also be important, both at baseline and as needed on follow-up. Any abnormality in these settings may be an indicator of underlying renal damage, and if this occurs, subsequent efforts should be made to prevent continued renal damage. In addition, treating hypertension and proteinuria (both of which contribute to further renal deterioration) represents an additional front in the prevention of ESRD. ACE-I or angiotensin receptor blockade should be considered a first-line therapy in patients with hypertension or proteinuria related to VUR. Prompt initiation of antibiotics in the setting of acute pyelonephritis also helps limit renal scar formation. Finally, multiple options exist in addressing and treating VUR (which will be discussed in later sections), with the hopes of minimizing the development and worsening of reflux nephropathy.

Select Populations at High Risk for VUR and VUR Sequelae

Certain populations are at risk for VUR-related morbidity as adults. Three such notable groups are pregnant women, those who have undergone renal transplant, and those with spina bifida.

Pregnancy

Pregnancy is associated with physiologic dilation of the urinary tract due to increased progesterone and decreased peristalsis [171], which may predispose to bacteriuria, symptomatic UTI, and premature labor [172, 173]. Reflux has also been proposed to occur more commonly in pregnancy than subsequently [174]. In addition, women demonstrate a decreased inflammatory response during pregnancy [175]. These changes may predispose pregnant women with VUR to UTI.

Further, pregnancy accelerates renal deterioration in other chronic renal diseases [28, 176, 177], and the same holds true in patients with VUR. Increased urinary filtration is seen in pregnancy, and this higher glomerular filtration rate may contribute to glomerular overload, hyperfiltration, segmental hyalinosis, and sclerosis in patients with baseline impairment [178]. In addition to this risk of renal deterioration, those with baseline reflux nephropathy are at risk for gestational hypertension, preeclampsia, and eclampsia [179–182]. Overall, roughly half of pregnant women with VUR develop complications during pregnancy [183].

Becker et al. [181] presented the first case series on pregnancy in reflux nephropathy: he identified six women with reflux nephropathy and renal impairment that experienced pregnancy into the second trimester or beyond. Renal deterioration was seen in all six during pregnancy and afterwards, with two-thirds developing ESRD by 2 years postpartum and two-thirds experiencing periods of accelerated hypertension, which was deemed more markedly accelerated than those that had not been pregnant.

Pregnancy-related complications from VUR depend primarily on baseline renal function. One of the largest studies to look at pregnancy outcomes in women with VUR evaluated 345 pregnancies in 137 women with reflux nephropathy [183]. Overall fetal loss was 14 %. Though the presence of VUR itself did not increase the risk of fetal loss or maternal complications, impaired renal function prior to conception did. Fetal loss was significantly higher (18 % vs. 8 %) after 12 weeks' gestation in women with renal insufficiency. Maternal complications were also significantly more common in women with renal insufficiency and in those with bilateral renal scarring: particularly, rates of preeclampsia were higher in women with bilateral compared with unilateral renal scarring (24 % vs. 7 %).

Other studies have further found baseline renal impairment to be a risk factor for adverse outcomes during pregnancy. Women with mild to moderate renal impairment prior to pregnancy have a 12.7 and 19.8 times relative risk of renal deterioration during pregnancy, respectively [184]. Risk of prematurity also increases in women with baseline impaired renal function [184]. Whereas women with mild renal insufficiency have generally fair fetal prognosis, those with severe renal insufficiency, renal scarring, and hypertension tend to have more guarded fetal prognosis or maternal progression to renal failure [185, 186].

However, women with renal scarring—regardless of the continued presence of VUR—are the ones at greatest risk for morbidity during pregnancy [187]. Rates of hypertension are 31–42 % in pregnant women with scarring [95, 188, 189]. Preeclampsia is seen in 10–14 % with renal scarring, compared with the 0.8–7 % seen in the general population [187–190]. Of note, preexisting hypertension is also a strong risk factor for preeclampsia (42 % vs. 14 %) [184]. Women with scarring also have a 20 % likelihood of delivering a baby of low birth weight. Finally, scarring predisposes to acute renal failure and premature birth weight.

In contrast, the presence of VUR itself does not portend as much morbidity. Women with VUR and no renal scars generally do not get gestational hypertension, preeclampsia, eclampsia, or fetal morbidity at rates higher than in the general population [183]. However, they are at increased risk for UTI during pregnancy, regardless of prior surgical correction. UTI in patients with uncorrected VUR occurs in 15 % of pregnancies [191]. However, this elevated UTI risk alone does not confer the same risks of preeclampsia, premature birth weight, and acute renal failure as does the presence of renal scarring [186]. Of note, though, Mansfield et al. [191] found a spontaneous fetal loss rate of 18 % in those with uncorrected VUR.

Thus, risk stratification in women with uncorrected VUR should center on the presence of renal impairment, scars, and hypertension and not the presence of VUR or UTI alone. By extension, scar formation should be an important outcome measure in deciding on treatment strategies for younger female patients with reflux.

While uncorrected VUR has its known sequelae, even when surgically corrected, women with a history of VUR remain at risk for morbidity. Of note, they are at substantial risk for the development of asymptomatic bacteriuria and UTI, and it's possible that their risk for UTI remains the same or even higher after surgery [187, 191]. High rates of asymptomatic bacteriuria are seen in 57–65 % of pregnant women who had undergone corrective surgery for VUR, which is in contrast to the 29 % rate of bacteriuria in these women when not pregnant [183, 192, 193]. In comparison, the rate of asymptomatic bacteriuria in pregnant and nonpregnant women alike is 3–5 % [194, 195]. Roughly 20–40 % of women with asymptomatic bacteriuria in pregnancy will develop a symptomatic UTI if left untreated [196, 197]. Asymptomatic bacteriuria may also be associated with low birth weight, preterm delivery, and fetal loss in the general obstetric literature [194], but this relationship has not been studied specifically in adult women with VUR.

On extended follow-up of patients with surgically corrected VUR in childhood, older studies identified a 32–65 % rate of women with symptomatic UTI in pregnancy [94, 186, 188, 189, 191, 192]. Today, urine screening during pregnancy is much more common, which reduces rates of symptomatic UTI by 80–90 % [198]. Likely as a result, modern series report a 17–30 % rate of symptomatic UTI in this population [199–201]. In contrast, the rates of symptomatic UTI in pregnancy in the general population are roughly the same at 3–7 % [183, 191].

Rates of pyelonephritis are also higher, even despite previous surgical correction of VUR (3–37 % vs. 1–2 % for women without such a history) [95, 186, 188, 191, 200–202]. These women are at significantly higher risk for spontaneous fetal loss compared with their surgically corrected counterparts that do not develop pyelonephritis in pregnancy (50 % vs. 19 %) and compared with women who develop lower UTI only. They are additionally at risk for multiple spontaneous abortions [201].

Risk factors for bacteriuria and UTI during pregnancy in women with surgically corrected VUR include prior UTI, renal scarring, and abnormal split differential renal function of ≤30 % [188, 201]. Renal scarring may be associated with a 60 % rate of bacteriuria and a 42 % rate of symptomatic UTI during pregnancy, compared with a 22 % rate of UTI during pregnancy in those without scarring [186, 188]. Antibiotic prophylaxis may be a reasonable management strategy during pregnancy in select patients.

Additional morbidities are also higher in women that have undergone VUR correction. Preeclampsia is seen in up to 38 % [199, 200] and eclampsia as commonly as 10 % in some series [94, 186, 199]. They also have a 9–27 % risk of spontaneous abortion [94, 183, 186, 191, 193, 200, 201], compared with an 8–12 % in the general population [203–205]. Fetal loss is higher (63 %) among women with elevated creatinine and even more so (75 %) in the setting of concomitant hypertension [182]. Pregnancy after surgical correction may rarely require renal drainage for obstruction or result in permanent renal failure (4 % and 2 %, respectively) [200]. In particular, those who had undergone Politano-Leadbetter procedures may be at greatest risk for obstructive hydronephrosis and resultant renal failure during pregnancy [193].

Finally, those with a history of VUR should be counseled that their children have higher risks of VUR, and their offspring should be considered for evaluation. However, risk estimates vary widely. Early studies placed the risk of VUR in the offspring of a proband with VUR at 66 % [206]. One study found VUR on VCUG in 43 % of screened infants whose mothers had VUR [184]. Another population-based multicenter study in England found among women with assumed or confirmed histories of VUR a 22.7 % risk of VUR in their children when screened with VCUG or RBUS [207]. In families with at least one proband with a history of VUR and a history of consanguinity, the risk of VUR in a child

increased to 31 %. VUR is likely transmitted in an autosomal dominant fashion with incomplete penetrance [2, 184, 208, 209]. Scott et al. [207] found equal rates of VUR among male and female offspring and surmised higher rates of VUR detection in females to be due to higher rates of UTI in girls.

Some have recommended surgical correction of VUR in adult women with scarring prior to pregnancy in order to reduce maternal and fetal morbidity. Without the presence of reflux nephropathy, the main peripartum risk of VUR centers around the increased development of UTI, including pyelonephritis. However, there is insufficient evidence to say that VUR alone in the absence of scarring or reflux nephropathy would benefit from pre-pregnancy correction. Women with a history of VUR—surgically corrected or not—should be considered for antibiotic prophylaxis, particularly if scarring is present. Regular monitoring for UTI with urinalysis and cultures should be undertaken as well, with emphasis on preventing or aggressively treating episodes of pyelonephritis. Finally, women with a history of reflux—particularly those with reflux nephropathy, including scarring and renal impairment—should be counseled regarding potential renal, hypertensive, and fetal morbidities that may occur with pregnancy.

Renal Transplant

In patients who have undergone renal transplant, VUR may be primary or secondary, either into the transplant or native kidneys [21]. Recurrent UTI due to VUR in a potential transplant recipient may necessitate pre-transplant nephroureterectomy in order to minimize UTI risk post-transplant [210].

Post-transplant, VUR into the transplant kidney may commonly occur as well. The decision to perform a refluxing vs. a nonrefluxing anastomosis in transplant recipients is an ongoing debate. Many transplant surgeons prefer a refluxing to an obstructed anastomosis, and creating an antirefluxing anastomosis may add technical challenge and time to the procedure. In the adult population, there is insufficient data to support universally performing a nonrefluxing anastomosis, as despite wide ranges of VUR in the adult transplant kidney (1–86 %) [211–215], rates of post-transplant pyelonephritis are relatively low (0.1–4.7 %) [216–221]. Further, the presence of VUR has not been found to affect graft function or survival [215]. However, in pediatric renal transplant patients, who have a 90 % incidence of UTI and a higher propensity for lower urinary tract dysfunction, a nonrefluxing anastomosis is favored. Rates of post-transplant VUR have improved from 79 % in older series, in which the Lich-Gregoir technique was utilized, to 9 % and 19 %, with the development of more modern extravesical and intravesical techniques, respectively [222–226]. VUR into transplant kidneys in pediatric patients predisposes to pyelonephritis (23–37 % vs. 0–5 % in those without VUR) and subsequent graft dysfunction. Younger children (i.e., less than 7 years old) and those with underlying bladder dysfunction are most notably at risk [226–228].

Regardless of technique of reimplantation, VUR in the renal transplant recipient becomes more prevalent with time [229]. Patients with lower urinary tract dysfunction generally present earlier post-transplant with VUR relative to patients without LUT dysfunction [226] and LUT dysfunction may, in fact, be a risk factor for post-transplant VUR development [225]. The true clinical significance of a refluxing anastomosis with respect to long-term graft function is controversial [218, 230, 231]. Some have found equivalent rates of rejection episodes compared with those without reflux [218]. However, others have cited concerns of graft decline and premature graft loss [232, 233].

Transplant patients presenting with UTI or recurrent pyelonephritis should undergo evaluation for VUR, with urinalysis, culture, creatinine, and VCUG [224, 225, 228, 234], with consideration for urodynamics if an underlying LUT dysfunction is suspected [226]. Some advocate antibiotic prophylaxis or observation for a single UTI in transplant patients [225]. However, recurrent infection may necessitate surgical correction, which decreases the risk of pyelonephritis and may protect against graft deterioration [123, 222, 235].

Open surgical correction, i.e. with transplant to native ureteroureterostomy or pyeloureterostomy, and redo transplant ureteric implant represent the "gold standard" for correction of VUR to the transplant kidney [224, 228]; however, revision surgery is technically challenging and has many potential complications, including obstruction, leakage, and graft loss [236, 237]. Endoscopic injection with Deflux® has met with success in 44–58 % of cases and may be improved overall to 79 % with a second injection attempt [238–240]. Correction rates as high as 90 % are attainable in endoscopic injection for low-grade VUR [239]. Success may be slightly lower than in native kidney VUR due to scar formation at the anastomotic site as well as ectopic ureteral orifice location that may both impair endoscopic needle approach and create increased orifice mobility [238].

Neurogenic Bladder

Patients with neurogenic bladder due to myelomeningocele (MMC) or other etiologies, such as posterior urethral valves, are at risk for progressive renal deterioration due to the presence of secondary VUR and increased risk of UTI [241, 242].

VUR and renal insufficiency are common in patients with MMC, with a 26 % incidence of VUR in the first year of life and a 50 % prevalence by age 9 [243]. Roughly 30–40 % of young adult patients with MMC develop some degree of renal dysfunction [241]. One Taiwanese study found roughly 15 % of patients with MMC developed ESRD by age 20 [244]. The presence of detrusor-sphincter dyssynergia portends a particularly poor prognosis on renal function: it has a strong association with resultant VUR and is one of the most important predictors of renal deterioration [245, 246]. Studies evaluating incidence of VUR, or the secondary effects of VUR, in older adult populations are not available. Both ureteral reimplantation [247–249] and subureteral injection [250, 251] in neurogenic bladders are more technically challenging than in patients with primary VUR, and both are generally met with lower rates of success.

VUR Detected in Adulthood

VUR was first identified as a pathologic entity in adulthood [252, 253] roughly a decade after its importance in childhood was recognized [14]. Currently, as most cases of VUR resolve or are corrected in childhood, present data on VUR in adulthood is limited. Theoretically, VUR in adulthood may occur for a variety of reasons: undetected VUR from childhood, de novo primary VUR, and de novo secondary VUR.

It is unclear whether primary VUR in adulthood is due to the same pathophysiology as in childhood and whether its development is de novo in adulthood or simply "silent" VUR detected later in life. Roughly 35 % of adults with VUR report a history of childhood UTI [91], while many report only recent symptom onset around the time of detection [254]. As the onset and duration are generally unknown, complications such as scarring and renal insufficiency only become apparent later in the disease process [21].

Primary VUR in adulthood is much more common in women by a factor of roughly 5–18 to 1 [31, 33–36, 38, 124, 252, 253, 255, 256]. This is in contrast to the relatively more equal sex distribution seen in VUR in childhood [33, 38, 159]. This may be due to women's greater likelihood of presenting with UTI symptoms (as they are at greater anatomic risk for UTI in general), with men's presentation generally more delayed until more advanced effects of reflux nephropathy ensue [257]. Alternatively, the exacerbation of hypertension and proteinuria in pregnancy among women with VUR may explain increased detection rates in women. In the 60- to 70-year-old age group, a greater proportion of patients with VUR are men, largely attributed to a higher incidence of secondary VUR due to bladder outlet obstruction [255, 258].

The most common signs and symptoms that lead to VUR diagnosis in adults are UTI (64 %), proteinuria (14 %), and asymptomatic bacteriuria (13 %) [257]. Most (87 %) have a history of UTI, although UTI onset and frequency are variable [257]. While one historical series cited a 50 % rate of VUR among adults with recurrent

pyelonephritis [162], that number is much likely lower at 2.3–9 % [259–261]. Rare presenting signs and symptoms include hypertension, flank or back pain, and renal failure (10 % each) [257].

Most women with VUR (70 %) present initially with UTI [256, 257], and some (14 %) present with aymptomatic bacteriuria [21, 257]. Women are 12 and 7 times more likely to have symptoms of lower and upper UTI, respectively [257]. When a history of UTI is absent, hypertension upon initiating contraceptive pills or in pregnancy may be another common scenario of presentation in women. Between 5 and 33 % of women present in the setting of pregnancy-related complications [35, 39, 124, 182, 183, 256, 257, 262]. Proteinuria and renal insufficiency are much less frequent initial findings in women, seen in 10 % and 7 %, respectively, but may be present in as many as 17 % and 13 %, respectively, upon further evaluation [257].

Conversely, men more commonly present with symptoms of nephropathy, such as hypertension, proteinuria (37 %), and impaired renal function (31 %), and less frequently with complaints of UTI (25 %) or asymptomatic bacteriuria (6 %) [256, 257, 263]. On evaluation, as many as 56 % and 44 % of men have impaired renal function and proteinuria, respectively. Men also are commonly diagnosed incidentally when being evaluated for other urinary complaints [262].

In adult patients presenting with VUR, up to 89 % demonstrate renal scarring (depending on modality of presentation). This is in contrast to the 42 % seen by Lahdes-Vasama et al. [96] of patients with VUR diagnosed in childhood and 30-year follow-up. Thus, VUR not detected until adulthood seems to allow for the interim, silent development of renal morbidity during this time. Roughly 18–37 % have evidence of renal function impairment. Risk factors for renal function impairment on multivariable analysis include elevated creatinine, proteinuria, hypertension, bilateral VUR, male sex, and recurrent UTI [36, 117, 256, 264].

Hypertension in adults diagnosed with VUR is relatively common at 13–56 %, usually falling between 30 and 40 %, with incidences varying widely depending on the definition of hypertension [31, 32, 34–40, 117, 124, 140, 256, 257, 265, 266]. This is higher than the incidence seen in children with VUR, likely representing other confounding factors that contribute to hypertension in adulthood, but also in part relating to the natural history of uncorrected VUR [152]. In the adult population, hypertension may be anywhere from 2.6 to 8 times more common in those with bilateral VUR [31, 35, 37, 117, 257], although others have found no differences in rates of hypertension between those with unilateral and bilateral VUR [32, 34, 38]. Hypertension is up to 4 times as common in those diagnosed over age 45 [257]. Hypertension and severity of hypertension is also increased among those with renal insufficiency [190, 257] and renal scarring [266]. In those presenting in early adulthood with bilateral scarring or a solitary kidney, by the time renal function deterioration is noted on serum creatinine level, there is a 92 % incidence of hypertension [190, 257]. Men and women with VUR in adulthood have relatively similar rates of hypertension at 44 % and 32 %, respectively [257]. The incidence of malignant hypertension is relatively low at less than 2 % [39, 257] and is generally described only in those with extensive renal damage [190].

Previously, VUR was a cause of ESRD in 5–16 % of adults with ESRD [17, 40, 117, 122–126], although that number is much lower presently at 0.22 % [130] due to successful strategies at detection and management. VUR-related ESRD may occur at any age but typically peaks in the third to fourth decade of life [267]. VUR as a cause of ESRD is more common in middle-aged women with ESRD than men (ages 34–65 years), but at other ages, ESRD due to VUR occurs at equal rates among the sexes [125]. El-Khatib et al. [256] found that in adults with VUR and reflux nephropathy, the presence of proteinuria represented the best predictor for progression to ESRD; the presence of VUR itself was not an independent predictor of ESRD development.

Evaluation of the Adult for VUR

No clinical guidelines exist for the evaluation of adult VUR as they do for children. Typically, imaging for the evaluation of UTI in an adult is

limited to those with complicated UTIs or immunocompromised patients [268]. Adult patients who experience pyelonephritis and who have a personal history of corrected VUR or family history of VUR may also be considered for evaluation [269]. Adult women of child-bearing age with acute pyelonephritis may be evaluated as well [270], as identification could allow for correction or other management that would minimize the risk of pregnancy-related complications. Additional indications for evaluation for VUR may include those with flank pain upon bladder filling and those preparing to undergo renal transplant and with a history of UTI. VUR may also be considered as a potentially reversible cause of hypertension in select cases, even in the presence of normal renal function [271].

As in children, VCUG may be utilized in adults to evaluate for the presence of VUR [255, 272]. In patients with negative VCUGs but a strong suspicion of VUR, several techniques have been utilized to detect occult VUR. These include cyclic VCUG (which relies on multiple cycles of emptying and filling) [273]; performance of VCUG during the acute infection, once proper antibiotic therapy is initiated [274]; and PIC cystography, which relies on Positioning the Instillation of Contrast at the ureteral orifice during cystoscopy [275]. Nuclear medicine studies may also be used to assess renal scarring. Strong consideration should be made to whether VUR presenting in adulthood is secondary to voiding dysfunction or neuropathic bladder, so urodynamics should always be considered for these patients.

The Rationale for VUR Management

Preventing episodes of pyelonpehritis and minimizing renal morbidity are the two major goals of VUR management. Management strategies may include the utilization of prophylactic antibiotics, prompt initiation of antibiotics for pyelonephritis once it develops (already discussed), surgical techniques to eliminate VUR, and correcting any underlying bowel bladder dysfunction (BBD).

Debate exists as to whether the progressive reflux nephropathy related to VUR is preventable with intervention. Traditional thinking espouses that VUR predisposes to pyelonephritis, which leads to progressive renal deterioration, and that more severe VUR leads to greater degrees of renal damage [62, 78, 168, 276]. This is the belief that is predominantly held regarding treatment of VUR and is the rationale for most attempts at risk stratification and management. Certain groups of patients fit this model, such as some female patients with mild to moderate reflux detected at a relatively later point, who go on to develop recurrent pyelonephritis and renal scarring [55, 58].

However, there is an alternative theory that maintains that the renal damage associated with VUR relates to underlying renal dysplasia. In this theory, renal damage exists prior to the development of UTI, and is thus progressive despite seemingly successful medical and surgical interventions that prevent pyelonephritis. This seems particularly true for certain subgroups, such as infant males with dilating VUR, i.e., grades III–V [55, 56, 59, 61, 62, 277–280]. These patients are known to progress to CKD [16, 86, 112, 281], and in this cohort, reflux nephropathy follows its own natural progression despite aggressive treatment or number of episodes of pyelonephritis [9, 55, 56, 103, 280, 282]. Studies from the 1980s in children demonstrated that surgery is ineffective in preventing renal damage [281, 283, 284]. Further, even after VUR resolves, whether by spontaneous resolution or surgical correction, renal function may deteriorate and new scars may form [284–286]. Discouragingly, despite more aggressive medical and surgical treatment paradigms of VUR in place since the 1960s, the rate of ESRD due to reflux nephropathy has remained unchanged [287, 288].

The need for treatment of VUR in adulthood is even more debatable. Certainly, symptomatic reflux that results in recurrent pyelonephritis, new renal scarring, or deteriorating renal function merits consideration for treatment [289]. Additionally, certain patients may be at increased risk for the sequelae of febrile UTI in adulthood, such as pregnant women [290].

However, the potential for benefit from surgical correction of VUR is unclear. There is inconclusive evidence that surgical correction reduces

the risk of pyelonephritis in pregnant women [187, 191], and even after correction, much morbidity stems from the presence of renal scars and renal impairment that has already been acquired. However, many still prefer surgical correction for women of child-bearing age. Additionally, adult kidneys are less susceptible to infection [291] and much less susceptible to scar formation after age 5 [292]. Kidneys have also achieved their growth potential by adulthood [290], and so the risk of impaired renal growth is moot. Finally, even the presence of severe renal scarring is not itself an absolute indication for surgical treatment, as correction for this indication has not been shown to provide any benefit in adult patients [37, 293].

Thus, despite decades of research on VUR and its management, much about the natural history of reflux nephropathy remains debated and incompletely known. While medical and surgical treatment of VUR is certainly legitimate, it is important to keep these controversies and limitations in mind in order to understand that reflux nephropathy may be progressive despite "successful" therapies for VUR and that not all VUR requires treatment in order to achieve VUR resolution or sequelae-free outcomes. It is this disease heterogeneity that makes treatment decisions so challenging.

Spontaneous Resolution

Most cases of childhood reflux either resolve or improve with age [107, 151, 294]. The 5-year likelihood of spontaneous resolution is excellent for low-grade VUR (82–90 % for grade I and 80 % for grade II), whereas dilating VUR less frequently resolves spontaneously (46 % for grade III, 30 % for grade IV, and 13 % for grade V) [295–299]. Resolution is much more likely and quicker in unilateral vs. bilateral cases [120, 297–299], although others have found conflicting results [5, 300, 301]. Reflux is also more likely to resolve spontaneously in boys than in girls, usually due to high rates of resolution of low-grade VUR in boys [5, 70, 299]. Further, 94 % of patients with normal bladder function will achieve spontaneous resolution, vs. 0 % without in one study [302]. Overall, roughly 10–40 % of cases of reflux will persist [290, 299].

Once children reach approximately age 5 or 6, when the likelihood of spontaneous resolution decreases substantially, there is considerable debate on optimal management of persistent reflux, ranging from continued prophylaxis, cessation of prophylaxis, and surgical intervention (open or endoscopic). Many will opt to correct higher grades of reflux or bilateral reflux at this point; yet, more controversial are the lower grades, for which surgical correction is not as clearly indicated. Further, while long-term antibiotic prophylaxis is generally well tolerated by patients, parents may grow weary of continued antibiotic prophylaxis, with inconvenience and cost becoming a nuisance, and compliance may become a concern. This may be particularly true for patients with relatively early diagnoses and prolonged duration on continuous antibiotic prophylaxis (CAP). Additionally, new renal scars may still form at this age. One study evaluating the cessation of antibiotics in children at this age with minimal UTI and scarring history found VUR resolution in 19.6 %, UTI in 11.8 % and no new scar formation when followed for a mean of 3.7 years [303]. However, long-term studies on the outcomes of antibiotic cessation in the setting of persistent reflux are not available. Further concerns in prolonged observation include the need for ongoing radiologic imaging, which may result in emotional and financial costs to patients and families [304]. Additional concerns exist over the potential for DNA damage and malignancy due to ionizing radiation [305]. Modern equipment and techniques have lowered but not eliminated this risk [306–310].

Just prior to the onset of puberty, spontaneous resolution becomes even less likely. Debate exists regarding the need for surgical intervention in low-grade reflux that persists on approach to puberty [311]. Lenaghan et al. [15] found a 27 % rate of resolution after age 14 years. In fact, the risk of pyelonephritis and new renal scar formation is low in this population, and this may reason in favor of antibiotic cessation, even if reflux persists. Conversely, while VUR may have a lower incidence of sequelae in adolescence, many note

the morbidity of VUR and reflux nephropathy in women who become pregnant. While it has not been conclusively established whether this morbidity relates to the ongoing presence of reflux or the already sustained renal insult, many opt to correct VUR in this cohort of girls, prior to their child-bearing years.

The management of persistent reflux into later childhood and adolescence remains controversial and varies with grade of reflux, laterality, presence of reflux nephropathy, occurrence of UTI while on or off CAP, patient gender as it relates to the potential for morbidity with the onset of sexual activity and with pregnancy later in life, and family preference. Several of these topics will be discussed in later sections.

Unlike childhood VUR, primary VUR and VUR detected in adulthood does not generally resolve with time [293], as the intramural distal ureter no longer elongates with growth [312].

Modalities of Treatment in Vesicoureteral Reflux

With reflux of infected urine representing an important cause of acquired renal scar, the most immediate concern in patients with VUR is UTI prevention. Many treatment options exist, all aimed at reducing the incidence of UTI—specifically febrile UTI. These are broadly centered on medical management, which includes prophylactic antibiotics, prompt initiation of therapeutic antibiotics, and optimization of BBD, as well as surgical correction with endoscopic, open, and robotic techniques. Medical and surgical options for managing hypertension may also be considered. Most literature on VUR treatment and outcomes are described for pediatric populations; however, the same techniques are utilized in adults.

Surgical Management: Ureteral Reimplantation

Open and robotic surgical correction of reflux is extremely successful, with an overall rate of 96–100 % in eliminating VUR [313, 314]. Complications are rare, with 2 % each demonstrating persistent reflux or obstruction and 3 % requiring additional surgeries [298]. Contralateral VUR may occur as well in roughly 10 % but very rarely requires surgical intervention [315].

While surgical correction very successfully eliminates VUR, longer follow-up has found relatively high rates of symptomatic UTI. Rates of symptomatic UTI range from 38 to 75 % on 9–41 year follow-up [94, 95, 155, 186, 191, 199, 201]. Rates of febrile UTI are also relatively high at 18 % and 16 % during the first and second decade after surgical correction, respectively.

This high rate of UTI on extended follow-up may be explained in part by women's varying susceptibility to UTI at different points in life. UTI rates are highest in year 1 of life, second-highest at ages 2 to 4, drop during later childhood and adolescence, and rise again between ages 18 and 22, with commencement of sexual activity [197, 316–318]. Marchand et al. [201] found UTI incidence to rise from 42 % prior to the onset of sexual activity to 61 % afterwards, with roughly three quarters representing lower UTI. Mansfield et al. [191] found a 10 % rate of UTI in childhood post-surgery, which increased to a 75 % rate of cystitis and a 30 % rate of pyelonephritis following the onset of sexual activity; in those that had not undergone surgical correction, 62 % developed cystitis, while 23 % went on to develop pyelonephritis. These rates are higher than the 25–35 % of women in the general population that develop UTI with the onset of sexual activity [197] and the 0.28 % rate of pyelonephritis in healthy women [319]. There is also evidence that women with recurrent UTIs after corrective surgery may have diminished uroepithelial defenses [155, 320]. Finally, the presence of renal scarring may be a risk factor for recurrent UTI development in this population [188].

Despite this high rate of UTI, Mor et al. [200] found that roughly half (51 %) of surgically corrected patients have no future sequelae. On follow-up, surgical correction appears to protect the kidneys reasonably well from new scar formation in several studies [286, 321–323]. However, additional comorbidity may be found in surgically corrected patients. Some have found

that 13–22 % may develop new renal scars long-term [200, 201, 324]. Further, 4–13 % may develop hypertension (as many as 18.5 % in those with bilateral renal scarring) [32, 200, 201, 325, 326]. Even malignant hypertension has been known to develop after VUR has been surgically corrected [327]. Additional less common long-term developments after surgical correction include renal calculi, proteinuria, and renal insufficiency [200].

Open surgical repair is more challenging in adults due to increased pelvic vascularity and the relatively deep, retropubic location of the bladder that develops with age [289, 328]. Studies of open surgical reimplantation in adulthood report lower success rates than in pediatric patients: success in eliminating VUR may range from 83 to 100 %, with similar rates of obstruction and other complications as is seen in children [329–331]. The techniques utilized are the same in adults and in children, although a robotic-assisted approach may facilitate access to deep pelvic structures in older patients. In adults, surgical intervention has been shown to decrease rates of pyelonephritis [289, 330, 332]. Surgery is also associated with improvement in flank pain in 94 % (vs. 8.5 % utilizing CAP), and consideration for anti-reflux surgery should be made for this indication [331, 333]. However, surgery was not found to affect proteinuria or to halt progressive renal deterioration in those found to have baseline dysfunction at diagnosis; in this setting, proteinuria represents a poor prognostic factor for future renal function [37, 293–331, 334, 335]. Thus, indications for definitive repair as an adult should generally revolve around improvement of flank pain and reduction in episodes of febrile UTI.

One notable challenge in patients that have undergone surgical correction of VUR is the need for subsequent ureteral access for endoscopic procedures. This may be particularly germaine in patients who have undergone Cohen cross-trigonal reimplantation, who have more greatly altered post-surgical anatomy. The long and more horizontally oriented submucosal tunnel may make retrograde access in ureteroscopy challenging and may hinder passage of stone fragments after shockwave lithotripsy [336]. A variety of techniques that facilitate ureteral access have been described, including percutaneous retrograde access and utilization of curved angiographic catheters and angled guide wires [336–341]. These techniques may be useful in ureteroscopy for stone disease, retrieval of migrated stents, and retrograde pyelogram for anatomic delineation, potentially avoiding the need for percutaneous procedures in select cases.

Endoscopic Management

Endoscopic treatment with subureteral injection of bulking agents, first described in 1981 [342], represents a minimally invasive option in the armamentarium of VUR treatment modalities. Many agents have been used historically. Some nonbiodegradable materials, such as polytetrafluoroethylene (PTFE) and silicone, were extremely successful in eliminating VUR and UTI [343, 344]. However, granuloma formation and particle migration raised concerns for autoimmune reactions and potential malignancy [345–351]. Materials with less controversial safety profiles (i.e., glutaraldehyde cross-linked bovine collagen), were developed, which were biodegradable, caused minimal tissue reaction and did not migrate. While initial success rates were high [352–355], long-term durability ranged from mediocre [355, 356] to remarkably poor [357]. Results in secondary VUR were additionally lackluster [355, 358].

In 2001, the Food and Drug Administration approved dextranomer/hyaluronic acid copolymer (Deflux®, Oceana Therapeutics Ltd., Edison, NJ, USA) for endoscopic subureteric injection for the treatment of grades II–IV VUR; at the time of this publication, Deflux® is the only approved substance in the USA for this indication. Deflux® is biodegradable, non-immunogenic, noncarcinogenic, does not migrate, has no known associated adverse reactions, and has demonstrated durable results [359–361].

Meta-analysis of all types of injectables, including Deflux®, has been conducted in predominantly pediatric cohorts. Resolution rates overall are 77 % [251], with success rates of 72–81 % for grades I–III and 51–63 % for grades IV and V [250, 251]. Overall success rates may

be as high as 85 % with repeat injections [250]. Subureteric bulking agents are also successful in resolving VUR after failed open reimplant in 65–66 % of cases [250, 251]. In neurogenic bladders with accompanying secondary VUR, Deflux® is generally less successful, with a 50–69 % initial success rate that drops to 25 % when followed to a median of 4.5 years [250, 251, 362]. In these cases, ureteral reimplant with appropriate bladder management is adviseable [363]. Following Deflux® injection, rates of pyelonephritis and cystitis are low at 0.7 % and 6 %, respectively, although these results are only with short-term follow-up [250].

On longer follow-up, some have found low efficacy at 1 year, ranging from 46 to 68 % [364, 365], which may be technique related. Others have found 78.5 % efficacy at 3 years [356], even up to 87 % at 2–5 years [366]. Of those deemed initially successful, 21–26 % may recur at 1–3 years [365]. Recurrence should be suspected with the development of febrile UTI, which is associated with VUR recurrence in 47–83 % on reinvestigation [367–369]. Long-term, endoscopic injection may reduce renal scar formation in those with mild baseline scarring [367, 370]. However, it has not been found to be more effective in reducing new scar formation compared with surveillance or continuous antibiotic therapy [371].

Knowing the true long-term durability of Deflux® and other injectables is difficult, as post-procedure VCUG and long-term follow-up are both uncommon. Deflux® was also FDA approved relatively recently, and durability will be learned with time. Further, various definitions for success are utilized, including resolution after initial injection; resolution after repeat injection; VUR downgrading, i.e., from dilating to non-dilating, and infection-free status. These limitations provide support for following endoscopically treated patients beyond the initial success period. Further, those seeing patients that had undergone previous injection therapy should be aware of the limited data on long-term durability and should initiate reevaluation should febrile-UTI recur.

Whereas subureteric injection of bulking agents in children is successful in 73 %, that number is slightly lower at 65 % in adults similarly treated [250]. Early studies utilizing collagen injection demonstrated exceedingly low resolution rates of initial injection of 40 % at 24 months, with 44 % requiring reinjection [358]. However, more recent studies utilizing Deflux® report success rates of 69–91 %, with an 81–93 % rate of resolution with repeat injection [269, 372–375]. Success rates are higher with lower grades of VUR, as is the case in treatment of children [372]. The relatively high success rates and simplicity of minimally invasive endoscopic treatment make subureteric injection an appealing option for adults.

Additionally, consideration should be given to subureteric injection therapy for patients with unexplained flank pain and low-grade reflux, as this therapy may prove both diagnostic and therapeutic in a group of patients with a common symptom that can be explained by many etiologies.

Considerations for Medical Management in Adulthood

Medical management of VUR focuses on CAP, aggressive treatment of UTI, and minimization of BBD while awaiting VUR resolution.

Most literature on CAP relates to its use in children. CAP is more effective than placebo [376–378] and as effective as surgery [83, 84, 281, 284, 379, 380] in preventing UTI, with a 25–38 % vs. 32–39 % breakthrough UTI rate over 5 years, respectively [285, 297]. However, compared with surgical management, rates of febrile UTI over time are higher with CAP: 21 % vs. 8–10 % [45, 84, 281, 284, 296, 300, 381, 382]. Many practice guidelines advise the use of CAP in children with VUR [296, 298, 383]. CAP is generally used during the first few years of life; it is often ceased at ages 5–8 if children remain free of infection, free of new scar formation, and display normal voiding patterns, as rates of subsequent UTI are low and new renal scar formation minimal or absent [303, 384–386]. This management strategy is likely facilitated by the fact that many instances of reflux spontaneously resolve over time and the fact that scars are less likely to form in older children [292, 387].

However, the ability of antibiotic prophylaxis to protect against renal scarring is controversial [3, 388]. In most investigations, CAP has not proved effective in decreasing the incidence of renal scarring [378, 389–394], although some have shown CAP's equivalence with surgery with respect to renal function, renal growth, and renal scar formation [284, 285]. Others [298, 377, 379, 395–397] have further corroborated that while surgery may reduce rates of febrile UTI compared with CAP, it demonstrates equivalence with respect to renal growth and renal scar formation. CAP may be most effective in preventing renal scar in the setting of dilating VUR, when compared with surveillance and endoscopic therapy [371]. In non-dilating VUR, though, CAP does not appear to provide the same benefit [391, 392, 394].

In addition to its questionable benefit in preventing scar formation, long-term antibiotic prophylaxis is not completely benign. Prolonged antibiosis may be associated with the emergence of resistant bacterial strains, breakthrough UTIs, and notable cost [377, 392, 393, 398–404]. Compliance rates, typically 66–69 % in children [405, 406] and possibly as low as 31 % [401], have not been evaluated in the adult population with VUR. CAP is also associated with high rates of loss to follow-up. Further, roughly 10 % of patients on CAP will develop adverse reactions. These are usually limited to the first 6 months and are mostly self-limited (i.e., GI upset and rash), although rarely, hepatotoxicity, hematologic complications, and Stevens–Johnson syndrome with sulfa agents can develop [407–409].

In adults, the benefits of CAP are more abated. CAP reduces episodes of acute pyelonephritis, in adults; however, over a 16-year follow-up period, ureteral reimplant is more effective in reducing pyelonephritis than CAP (33 % vs. 72 %, respectively) [331]. Rates of overall UTI, though, are similar. Adults also have a decreased propensity for scar formation, and the ability of CAP to prevent new scars in this population is less well defined. Finally, CAP may serve as a temporizing measure in children while awaiting spontaneous resolution of VUR. In adults, whose VUR is much less likely to resolve spontaneously, the duration of treatment could theoretically span decades, especially if initiated in young adulthood.

Thus, as a long-term strategy, CAP is less practical in adults, especially when one considers the relative ease of definitive endoscopic management. Certainly, UTI development despite antibiotic prophylaxis is a strong indication for more definitive intervention [332]. Further, in young women likely to become pregnant, surgery is often preferred [330]. However, CAP may be considered in select adult populations at risk for recurrent UTI or its consequent morbidity or in those requiring a temporizing solution, patients that are already pregnant or those awaiting definitive intervention.

Bowel Bladder Dysfunction and VUR

The association between BBD and VUR in childhood is well-known. Roughly 1/2–1/3 of children with BBD have VUR [410–413], and slightly greater than 1/2 of children with VUR have BBD [7]. The presence of BBD portends a greater risk of febrile UTI and a lower likelihood of spontaneous resolution of VUR [414]. BBD also undermines success following ureteral reimplant [415] and endoscopic injection [291].

The association between VUR and voiding dysfunction continues into adulthood, and it is unclear whether this voiding dysfunction represents a cause or effect of the VUR. In middle-aged adults with a history of childhood VUR, 40 % have abnormal urine flow curves [416]. Higher rates of abnormal flow curves are present in those who had previously undergone an operation for their VUR (55 % vs. 30 %), with interrupted or weak flow representing the most common abnormal findings (seen in 45 % of all patients). Stress and urge incontinence among women are also more common in this group (35 % vs. 16 % and 20 % vs. 11 %, respectively), as are UTIs. Urodynamic findings in adult women with a history of VUR further demonstrate urethral sphincter overactivity (in 70 %), decreased bladder sensitivity, and large capacity bladders [417].

AUA Guidelines on the management of childhood VUR recommend treatment if there is evidence of BBD [291]. This may include behavioral therapy and biofeedback, alpha-blockers, anticholinergic medications, and constipation management. In children, behavioral modification along with antibiotic prophylaxis can resolve VUR in 36.8 % and downgrade it in an additional 21.1 % [418]. The addition of anticholinergics can resolve VUR in up to 45 % [419]. VUR resolution with these methods yields a decrease in breakthrough UTI [410, 418]. Further, antibiotic prophylaxis, anticholinergic medication, biofeedback, and psychological counseling in various combinations may eliminate infection in 64 % and resolve VUR in 53 % [420].

In contrast, there is debate as to whether treating BBD affects rates of spontaneous resolution in adulthood [299, 421–423]. Despite its prevalence, no guidelines exist for assessing and managing BBD in adults with VUR. Practitioners should have a high index of suspicion for BBD when evaluating adult patients and should develop treatment strategies specifically aimed at BBD if it is detected.

Adjunct Surgical Treatment for Hypertension

In cases of VUR-related hypertension requiring extensive antihypertensive therapy, nephrectomy or partial nephrectomy of the scarred atrophic renal unit may be considered, as this may alleviate the renin–angiotensin–aldosterone mediated process. Tash et al. [105] demonstrated success of partial nephrectomy in treating select cases of renin-mediated hypertension in patients with reflux nephropathy and focal renal hypoplasia (i.e., Ask-Upmark kidney), which may represent a similar pathology. However, one must weigh the risks of further renal compromise in these patients already at risk for renal impairment. In this scenario, nephrectomy should be reserved only for patients with uncontrolled or malignant hypertension [138].

Conclusions

VUR, while generally considered a disease of childhood, has implications into adulthood. While resolution of VUR is highly attainable, many patients sustain renal and systemic effects prior to correction or resolution. Further, morbidity may accrue even after resolution and may be exacerbated later in life. VUR management paradigms are remarkably different today than in decades past, and morbidity from this disease may be greatly reduced in the future. Certainly, more prospective, long-term studies are needed to better understand sources of reducible morbidity in this patient population.

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Part V

Pediatric GU Cancer Survivorship

Adult Survivors of Pediatric Genitourinary Tumors

17

Sarah M. Lambert

Genitourinary tumors contribute to pediatric solid tumors. Wilms tumor, rhabdomyosarcoma, and germ cell tumors are the most common malignant genitourinary tumors in children. Although Wilms tumor is the most common primary malignant renal tumor of childhood, rhabdoid tumor, clear cell sarcoma of the kidney, renal cell carcinoma, and other lesions have been identified (Lowe 2000). These urologic tumors occur in boys and girls with Wilms tumor having a male: female ratio of 1:1 (Pappo 2000). The SEER database demonstrates a 5-year overall survival rate for 93–94 % for gonadal germ cell tumors in boys less than 20 years (Bernstein 1999). While this chapter will not focus on gonadal germ cell tumors, these boys also require long-term surveillance and follow-up. They are susceptible to tumor recurrence and long-term effects. These long-term effects are similar to young adults treated for germ cell tumors.

As survival rates improve for children with genitourinary malignancies, there are both men and women who are adult survivors of pediatric genitourinary tumors. Most of these tumors occur in infancy and childhood. Therefore surveillance and posttreatment effects often begin during childhood and adolescence but can persist and progress during adulthood. Currently, the 5-year overall survival rate for children with Wilms tumor is greater than 90 % (DM 2004). Children with genitourinary rhabdomyosarcoma have a 5-year overall survival rate of 80 % (Punyko 2005). According to SEER statistics, there are approximately 325,000 childhood cancer survivors in the United States. Therefore, approximately 1 in 1,000 Americans is a survivor of childhood cancer (American Academy of Pediatrics Section on Hematology/Oncology Children's Oncology Group 2009).

These favorable survival rates result from current multimodal treatment algorithms. Chemotherapy, radiation therapy, and surgical management are the mainstays of treatment for pediatric genitourinary tumors. Given the high rates of long-term survival and successful salvage therapies, an understanding of the late effects of treatment is essential to patients and caregivers. Current investigations aim to maximize survival rates while minimizing late effects and complications of treatment. These late effects include cardiac, pulmonary, orthopedic, endocrine, renal, genitourinary, and oncologic disease. The Children's Oncology Group (COG) has been instrumental in establishing guidelines for follow-up of pediatric cancer survivors. The recommendations are based upon risk of exposure to treatments such as alkylating chemotherapy, pelvic and central nervous system irradiation, and genitourinary or pelvic surgical intervention. This chapter focuses on the late effects associated with pediatric genitourinary tumors and the adult survivor.

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Wilms Tumor

Wilms tumor or nephroblastoma is the most common renal malignancy of childhood (Miller 1995). It accounts for 6–7 % of all childhood cancers. The annual incidence rate is approximately 7–10 cases per million (Bernstein 1999). Most Wilms tumors are detected in the toddler and preschool age group with a median age of 3.5 years. Wilms tumor is uncommon in infants and rare in neonates. Less than 2 % of Wilms tumors are detected in neonates less than 3 months of age (CD 2004). Wilms tumor is typically identified due to a palpable abdominal mass or less commonly gross hematuria and abdominal pain.

The genetics of Wilms tumor continues to be extensively examined. The *WT1* gene was the first gene identified in Wilms tumor. Currently, Wilms tumor can be associated with a genetic mutation of *WT1* at 11p13 or a mutation of *WT2* at 11p15. Most tumors result from a somatic mutation within tumor tissue but a small percentage result from germline mutations. Approximately 10 % of children with Wilms tumor have associated congenital syndromes. *WT1* mutations are found in children with Denys-Drash syndrome (DDS), Frasier syndrome, and WAGR (Wilms tumor, aniridia, genital anomalies, mental retardation) syndrome (Muto 2002).

WT2 mutations are found in children with Beckwith–Wiedemann syndrome (BWS). Children with other overgrowth syndromes such as Perlman, Simpson-Golabi-Behmel, and Sotos' syndrome are also at risk for Wilms tumor development (Porteus 2000).

The current management of Wilms tumor is derived from cooperative group studies including the National Wilms Tumor Study Group (NWTSG) within the Children's Oncology Group (COG), the International Society of Pediatric Oncology (SIOP), and the United Kingdom Children's Cancer Study Group (UKCCSG). The 5-year overall survival rate for children with Wilms tumor is greater than 90 % (DM 2004). The goals of NTWS-5 included improving survival and understanding risk factors such as loss of heterozygosity at 11p14, 16p, 1p, age at diagnosis, precursor lesions such as nephroblastomatosis, bilateral disease, and the association with congenital anomalies. The objective of this risk stratification is to improve overall and disease-free survival while minimizing acute and long-term treatment associated morbidity.

Current Wilms tumor in the United States begins with radical nephrectomy for most children. This practice differs from the SIOP protocol that begins with neoadjuvant chemotherapy. The overall survival rates between these protocols are very similar (Metzger 2005). Treatment regimens are selected based on risk stratification and include biological, pathological, and clinical parameters. Multimodal therapy involves surgical extirpation, chemotherapy, and radiotherapy. Chemotherapeutic agents include vincristine, dactinomycin, and doxorubicin. Other therapeutic agents include cyclophosphamide and etoposide when necessary.

Given the significant improvements in survival, emphasis on evaluation of long-term treatment-related adverse events is increasingly important. Adverse events associated with Wilms tumor treatment can be associated with chemotoxicity, radiotoxicity, and surgical complications. Adverse events described in Wilms tumor survivors include tissue hypoplasia, secondary malignancies, nephrologic, endocrinologic, urologic, orthopedic, cardiovascular, and pulmonary events. Long-term nephrologic events include glomerular dysfunction, tubular dysfunction, and hypertension. Incontinence, hemorrhagic cystitis, and recurrent cystitis are documented long-term urologic events. Fertility concerns include elevated follicle stimulating hormone, elevated luteinizing hormone, oligospermia, and azoospermia. Twenty-five-year follow-up from the Childhood Cancer Survivor Study documented a 65.4 % incidence of chronic health conditions with 24 % reporting severe chronic conditions. Of the specific conditions evaluated, survivors reported higher rates of congestive heart failure, renal failure, and hypertension with hazard ratios of 23.6 (95 % CI 10.8–51.5), 50.7 (95 % CI 14.5–177.4), and 8.2 (95 % CI 0.4–10.5) respectively. Exposure to cardiac radiotherapy significantly

increased the risk of congestive heart failure (Termuhlen 2011).

Children receiving doxorubicin as salvage therapy have a higher frequency of cardiac disease. Echographic evaluation of left ventricular function demonstrated increased end systolic wall stress suggestive of subclinical cardiac dysfunction in children exposed to doxorubicin versus children unexposed (Iarussi 2003). Evaluation of NTWS 1, 2, 3, 4 children demonstrated a 4.4 % cumulative frequency of congestive heart failure in children exposed to doxorubicin as initial therapy and a 17.4 % cumulative frequency in children treated with anthracyclines for relapse. The relative risk of congestive heart failure was also elevated in children receiving lung irradiation and left abdominal radiation. This risk is increased in children receiving both doxorubicin and cardiac radiotherapy (Green 2001; Termuhlen 2011).

Survivorship studies document that the majority of event-free survivors of unilateral Wilms tumor do not demonstrate severe renal dysfunction. Despite these data, renal disease does occur in certain populations of Wilms tumor survivors. A Cochrane review of six studies demonstrated a 0.5–18 % prevalence of chronic kidney disease in Wilms tumor survivors treated with unilateral nephrectomy (Knijnenburg 2013). Bilateral Wilms tumor presents a difficult challenge from an oncologic standpoint. Preoperative chemotherapy and nephron sparing surgery are often indicated for these children with partial nephrectomy as part of the operative armamentarium. This treatment shift has decreased the overall risk of renal failure from 16.4 % in NWTS-1-2 to 3.9 % in NWTS-4. Long-term follow-up does report significant morbidity with adults developing renal failure, requiring renal transplantation and developing secondary tumors (Aronson 2011). Bilateral nephrectomy is the most prevalent etiology for end-stage disease. Other etiologies include radiation nephritis, DDS, chemotherapy toxicity, and surgical complications (Ritchey 1996). Children with WAGR and other associated genitourinary anomalies are also at elevated risk for end-stage renal disease. Children with DDS have a greater than 50 % incidence of end-stage renal failure (Breslow 2005). Long-term effects include decreased glomerular filtration rate, microalbuminuria, and hypertension. Hypertension and prehypertension are commonly found in patients with Wilms tumor. A recent study sought to evaluate the blood pressure profile and cardiac diastolic function in adolescent survivors of unilateral Wilms in remission. Ambulatory blood pressure monitoring demonstrated a 20 % prevalence of hypertension. Specifically, daytime systolic blood pressure, nighttime systolic blood pressure, and nighttime diastolic pressure measurements were increased among Wilms tumor survivors compared to healthy matched controls (Elli 2013). Children who receive chemotherapy and radiotherapy are at highest risk for hypertension and renal insufficiency. This particular group of children is also at an elevated risk for growth hormone deficiency and cardiovascular disease (Geenen 2010).

The risk of adverse events is elevated in children receiving radiotherapy versus children receiving surgery and chemotherapy alone. A retrospective evaluation of Wilms tumor survivors from the Netherlands reviewed long-term effects of radiotherapy in children treated for Wilms tumor. This study documented radiation enteritis and colonic obstruction in the radiation field. Cardiovascular, pulmonary, secondary malignancy, orthopedic and fertility events were more common in the radiotherapy group. In addition, diabetes mellitus only occurred in children treated with radiotherapy. Secondary malignancies included basal cell carcinoma, malignant histiocytoma, melanoma, osteosarcoma, and thyroid carcinoma. In this series, 68 % of Wilms tumor survivors had a minimal of one adverse event and 21 % of survivors had five or more adverse events. When stratified by radiotherapy exposure, 50 % of unexposed survivors developed an adverse event in comparison to 90 % of survivors treated with radiotherapy at a median follow-up of 18.9 years (Van Duk 2010) The childhood cancer survivor study 25-year follow-up of Wilms tumor reports similar findings with a cumulative incidence of 3 % for secondary malignancy. Soft tissue sarcomas followed by breast cancer were the most commonly identified secondary malignancies.

Most concerning, is the increasing incidence of secondary malignancy with increased length of follow-up (Termuhlen 2011). Results from the British Childhood Cancer Survivor Study documented a less than 1 % incidence of secondary malignancy. Secondary malignancies included solid tumors, lymphoma, basal cell carcinoma, and acute myeloid leukemia. Most tumors occurred in the thoracic, abdominal, or pelvic area and within the radiation field. Seventy-five percent of solid tumors were associated with radiotherapy (Taylor 2008). Efforts to limit radiation exposure have lead to a decrease in radiotherapy for Wilms tumor from 1973 to 2008; 75 % of children with Wilms tumor were treated with radiation in 1973 in contrast to 53 % in 2008 (Jairam 2013). An international collaborative study including North American, British, and Nordic patients demonstrated a 6.7 % cumulative incidence of secondary malignancy at 40 years of age (Breslow 2010).

The successful multimodal treatment of Wilms tumor results in significant numbers of long-term survivors. Many of these children can look forward to a healthy adulthood. Understanding the subgroups at higher risk of long-term complications is essential. Those children with WT-1 or WT-2-associated symptoms often have other manifestations of disease that can affect renal and endocrine function. Renal function should be monitored throughout adulthood and evaluation for hypertension should be pursued. In children receiving chemotherapy, the risk for infertility should be acknowledged. Men with difficulties attempting to conceive should be assessed for oligospermia or azoospermia. If a Wilms tumor survivor has received doxorubicin, the risk for cardiac dysfunction should be noted and included in any preoperative evaluation. Children requiring radiotherapy are also at elevated risk for posttreatment complications and long-term radiation effects. Finally, the risk for secondary malignancy requires active surveillance. Surveillance protocols are based upon the disease and specific treatment received. Children treated with doxorubicin should have cardiac monitoring with echocardiograms and complete blood counts. Exposure to etoposide also requires complete blood count monitoring yearly. Due to the endocrine and fertility risks associated with alkylating agents, follicle stimulating hormone, luteinizing hormone, estradiol (women), semen analysis, urinalysis, and complete blood count are often indicated in exposed children. Children who underwent radiotherapy to the abdomen or flank should have echocardiograms, liver function tests, colonoscopy, urinalysis, basic metabolic panel included in their long-term follow-up (Sadak 2013).

Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft tissue malignancy in children. Wilms tumor and neuroblastoma are the only more common pediatric solid tumors. In children, genitourinary rhabdomyosarcoma comprises approximately 25 % of rhabdomyosarcoma sites (Howlader 2010). These tumors can present with a palpable abdominal mass, gross hematuria, or lower urinary tract symptoms such as frequency. Paratesticular rhabdomyosarcoma presents as a painless scrotal mass. Rhabdomyosarcoma is also associated with genetic syndromes including Li-Fraumeni syndrome and neurofibromatosis (Malkin 1990). There is a bimodal age distribution for rhabdomyosarcoma with the first peak occurring in infancy and a second peak in adolescence. Due to this bimodal distribution, adult providers may directly encounter teenagers and young adults with primary genitourinary rhabdomyosarcoma.

Tumor stage is highly predictive of survival and dictates the treatment regimen. The TNM staging system includes tumor site, tumor size, histology, nodal disease, and metastases (Lawrence 1997). Unfortunately children younger than 1 year of age or older than 10 years of age experience decreased overall survival even after adjustment for TNM stage. Rhabdomyosarcoma is treated with multimodal therapy including chemotherapy, radiotherapy, and extirpative surgery if indicated. In comparison to adults, genitourinary rhabdomyosarcoma in children is more responsive to chemotherapy and radiotherapy. Therefore immediate extirpative surgery is usually

not indicated. This knowledge guides therapy for infants and adolescents. Pelvic exenteration is reserved for children with residual viable tumor after chemotherapy and radiotherapy. When cystectomy or partial cystectomy is indicated, children can undergo vesicostomy, ileal conduit, end cutaneous ureterostomies, or continent urinary diversion in selected patients. Long-term complications of pelvic exenteration include, ureteral stricture, hydrone (Michalkiewicz 1997) phrosis, bowel obstruction, fistula, and lymphedema.

Primary chemotherapy for most children utilizes vincristine, dactinomycin, and cyclophosphamide. Alternate regimens can include other chemotherapeutic agents such as irinotecan, topotecan, ifosfamide, and etoposide. Long-term effects of chemotherapy are recognized in many childhood survivors of sarcoma. Exposure to alkylating agents such as cyclophosphamide is associated with a high risk of infertility due to gonadal toxicity. A study of men exposed to high dose cyclophosphamide as children documented 58.8 % azoospermia, and 29.4 % oligospermia with only 11.8 % of men having normal semen analyses. Seventy-one percent of these men had elevated follicle stimulating hormone levels. While testosterone levels were normal in 94 % of men, luteinizing hormone levels were elevated in 40 % of men. These effects appear to be dose dependent thus the degree of severity depends on the exposure dose rather than age at exposure (Kenney 2001). Alkylating chemotherapy including cyclophosphamide and ifosfamide also adversely affect bladder function and can lead to hemorrhagic cystitis and chronic fibrosis. The potential for development of transitional cell carcinoma is also associated with cyclophosphamide exposure (Agarwala 2001).

Children with rhabdomyosarcoma are at increased risk for secondary malignancy post therapy. A review of secondary malignancies from the intergroup rhabdomyosarcoma study committee documented a 10-year cumulative incidence of 1.7 % for children enrolled in IRS I and II. Children receiving chemotherapy and radiotherapy were at highest risk. Additionally, chromosomal abnormalities such a Li-Fraumeni and neurofibromatosis were found in many of these children (Heyn 1993). A similar European review documented a 10-year cumulative incidence of 2.4 % for children enrolled in IRS III, IV pilot and IV. Sarcomas were the most prevalent secondary malignancies. In this review, disease severity at presentation also correlated with risk for late adverse events (Sung 2004). Compared to siblings, childhood cancer survivors were half as likely to sire a pregnancy. Radiotherapy and alkylating agent exposure were the major identifiable risk factors for decreased pregnancy rates. Men without high-risk exposures were equally likely to sire a pregnancy as the siblings (Green 2010).

Radiotherapy is indicated in almost all children with rhabdomyosarcoma unless the tumor is completely resected with favorable histology (Jairam 2013).

Children with genitourinary rhabdomyosarcoma have a 5-year overall survival rate of 80 % (Punyko 2005). Since the 1970s, both the survival rate and the bladder preservation rate have been increasing. Much of this increase can be attributed to the use of radiotherapy. Despite this increase in survival, growth and developmental retardation are a significant side effect of radiotherapy in prepubertal pediatric patients. Long-term effects of radiotherapy include urologic, gastrointestinal, pulmonary, cardiac, orthopedic, and neurocognitive dysfunction. Pelvic radiotherapy exposure is associated with an increased risk of osteonecrosis of the hip, urethral fistula, and colonic fistula (Sharma Arindam Kurtz 2014). Additionally, survivors must be counseled regarding infertility and secondary malignancies (Jairam 2013). Even the lowest effective radiotherapy doses can cause urinary incontinence, infertility, bowel injury, and pelvic skeletal deformity (Womer 2006).

Embryonal rhabdomyosarcoma is the most common histological type and includes sarcoma botryoides found in the bladder and vagina. Embryonal rhabdomyosarcoma is associated with an improved prognosis and a lower rate of local recurrence than the alveolar subtype. Prognostic indicators include stage, tumor size, histology, and age. In rhabdomyosarcoma, age less than 1 year or greater than 10 years are associated with a worse prognosis (Rodeberg 2011; Malempati

2011). The first Intergroup Rhabdomyosarcoma Study from 1972 to 1978 documented an overall survival for nonmetastatic rhabdomyosarcoma of 78 % and bladder preservation rate of 22 %. These data contrast with an 82 % survival rate at 6 years and a bladder preservation rate of 55 % in event-free survivors today. Of these children who underwent partial cystectomy 94 % ultimately required a subsequent procedure including repeat partial cystectomy and ureterouretrostomy (Arndt C, Does bladder preservation (as a surgical principle) lead to retaining bladder function in bladder/prostate rhabdomyosarcoma? Results from Intergroup Rhabdomyosarcoma Study IV 2004).

Bladder and prostatic rhabdomyosarcoma sites are associated with long-term bladder lower urinary tract dysfunction. Results from the Intergroup Rhabdomyosarcoma Study IV (IRS) demonstrated bladder preservation in 55 % of event-free survivors. Forty percent of children were documented to have normal bladder function (Arndt 2004). Other authors report normal bladder function or minor alterations in function after chemotherapy and radiation. However, one of these patients required a cystectomy due to severe bladder dysfunction (Soler 2005). Others report children often require radical cystectomy and urinary diversion despite chemotherapy and radiotherapy (Kamii 1994). Children with urinary diversions due to extirpative surgery for rhabdomyosarcoma are at risk for complications of urinary diversion such as stomal stenosis, stomal irritation, urinary leakage, obstruction, urinary reflux, urinary tract infection, diarrhea, nephrolithiasis, B12 deficiency, and sexual dysfunction. Orthotopic continent urinary diversion has also been described in children after extirpative surgery (Rigamonti 2006). These children are at risk for late complications associated with orthotopic or heterotopic continent reservoirs as they continue to mature into adulthood. These complications include reoperation, low bone mineral density, low B12 levels, and chronic diarrhea (Elshal 2012). Boys who undergo multimodal therapy including radical cystectomy are at risk for erectile dysfunction. The degree of dysfunction varies with approximately half of the boys have unsatisfactory erections while others appear to have normal erectile function and satisfaction. One boy had success with sildenafil therapy (Macedo 2010). Children with tumors located at the dome of the bladder are most likely to retain bladder function after partial cystectomy. Urodynamic evaluation after pelvic radiation demonstrated decreased bladder capacity and abnormal voiding patterns (Yeung 1994). Continued evaluation and management of lower urinary tract function is essential for rhabdomyosarcoma survivors.

Vaginal and uterine rhabdomyosarcoma commonly demonstrate embryonal histology and have an excellent prognosis (Waterhouse 2011). Despite the excellent prognosis, these girls are still at risk for lower urinary tract dysfunction and can even require extirpative surgical intervention. Most vaginal and uterine rhabdomyocarcomas present during infancy. Presentation can include an introital mass, vaginal bleeding, or vaginal discharge. Multimodal therapy has decreased the need for anterior pelvic exenteration. The IRS-IV study demonstrated a hysterectomy rate of 26 % (Arndt 2001). Despite this decrease, women with a history of pelvic rhabdomyosarcoma are at risk for long-term adverse effects. Some of these effects result from the operative oncologic intervention required including hysterectomy, complete or partial vaginectomy, complete or partial cystectomy, and oophorectomy. The median age of women in this series was 25 years. Over 50 % of these women experienced genitourinary late effects. The documented genitourinary late effects included vaginal stenosis, vesicovaginal fistula, ureteral obstruction, retroperitoneal fibrosis, neurogenic bladder, recurrent UTI, urinary incontinence, chronic pelvic pain, ovarian failure, and nephrolithiasis. Twelve percent of women developed secondary malignancy including adenocarincoma of the colon, cervical cancer, and pelvic osteosarcoma. Seventy-seven percent of women experienced endocrine late effects. These late effects required surgical intervention in 54 % of women. Surgical procedures included vaginal dilation, vaginal reconstruction, repair of ureteral

obstruction, vesicovaginal fistula repair, and intestinal stricture repair (Spunt 2005). A second European series specifically evaluating women with vulvar and vaginal rhabdomyosarcoma documented 20 % incidence of vaginal and urethral stenosis (Magne 2008).

Paratesticular rhabdomyosarcoma represents 7–10 % of genitourinary rhabdomyosarcoma with a peak age of 1–5 years at diagnosis (Weiner 1994). Unlike other genitourinary rhabdomyosarcomas, approximately 60–80 % of Paratesticular tumors are stage I at presentation (Wiener 2001). Overall, boys with paratesticular rhabdomyosarcoma have a good prognosis. Survival rates of 90 % can be anticipated with the use of current multimodal treatment protocols (Wiener 2001). Paratesticular rhabdomyosarcoma is initially managed with radical orchiectomy. Paratesticular rhabdomyosarcoma has a 90 % 5-year survival rate. Embryonal subtype comprises 90 % of paratesticular rhabdomyosarcoma and allows for less intensive chemotherapy regimens than the alveolar subtype (Ferrari 2004). Sixty to 80 % of boys with paratesticular rhabdomyosarcoma are stage I at presentation. According to Children's Oncology Group protocols, boys 10 years of age or older should undergo an ipsilateral retroperitoneal lymph node dissection (RPLND) to complete an accurate staging assessment. Boys older than 10 years at presentation are at increased risk of relapse in the retroperitoneum therefore RPLND prior to chemotherapy is essential (Wiener 2001). Boys with nodal disease require both chemotherapy and radiotherapy. RPLND for boys with paratesticular rhabdomyosarcoma carries similar risk to RPLND for germ cell tumors including intestinal obstruction, ejaculatory dysfunction, hydrocele, and lymphedema. Long-term follow-up of boys treated for paratesticular rhabdomyosarcoma have demonstrated additional risks of chronic diarrhea, hemorrhagic cystitis, urethral strictures, and urethritis. Over half of the men analyzed by Hyen and colleagues were noted to have elevated follicle stimulating hormone levels and azoospermia (Heyn 1992). Recently cooperative group studies are evaluating failure-free survival and morbidity including rates of secondary malignancies with the objective to reduce long-term morbidity given the increased survival rates (Arndt 2009). Due to these late effects, surveillance protocols are necessary for childhood rhabdomyosarcoma survivors. Children exposed to etoposide should have complete blood count monitoring yearly. Cyclophosphamide and ifosfamide treatment is associated with significant endocrine and fertility risks and therefore follicle stimulating hormone, luteinizing hormone, estradiol (women), semen analysis, urinalysis, and complete blood count should be considered. Children who underwent radiotherapy to the pelvis are also at risk for infertility and evaluation should be pursued if indicated (Sadak 2013). Children exposed to pelvic radiotherapy with gait abnormalities or osteonecrosis of the hip can require long-term orthopedic care.

Summary

The current management of Wilms tumor and rhabdomyosarcoma includes surgical, chemotherapeutic, and radiation therapies. The multimodal treatment protocols have advanced the care for children with childhood cancers. As a result, the numbers of adult cancer survivors is growing. The 5-year overall survival rate of 90 % and 80 % for children with Wilms tumor and rhabdomyosarcoma respectively contributes to these improving statistics (Punyko 2005). The approximately 325,000 childhood cancer survivors in the United States require long-term follow-up, surveillance, and treatment. One in 1,000 Americans is a survivor of childhood cancer and is susceptible to routine urologic conditions and particularly at risk for cardiac disease, renal dysfunction, surgical complications, infertility, and secondary malignancy (American Academy of Pediatrics Section on Hematology/Oncology Children's Oncology Group 2009). As these children mature into adulthood, adult urology providers become their primary urologic care providers. Understanding adult cancer survivors is essential to all practicing urologists.

Summary Points

1. Late events described in Wilms tumor survivors include tissue hypoplasia, secondary malignancies, nephrologic, endocrinologic, urologic, orthopedic, cardiovascular, and pulmonary events.
2. Twenty-five year follow-up from the Childhood Cancer Survivor Study documented a 65.4 % incidence of chronic health conditions with 24 % reporting severe chronic conditions. Follow-up recommendations for Wilms tumor survivors include:
   (a) Annual BMP, UA/protein, blood pressure monitoring.
   (b) Screening for fertility concerns, and appropriate diagnostic testing as warranted.
   (c) Doxyrubicin: symptomatic screening, periodic echocardiogram, annual EKG, referral to cardiology as appropriate.
   (d) Cyclophosphamide: hematuria/LUTS screening, UA, periodic cystoscopy or as warranted by symptoms.
   (e) Etoposide: annual CBC.
   (f) Alkylating agents: FSH, LH, estradiol or semen analysis as warranted by screening and annual CBC.
   (g) Abdominal/flank radiation: GI symptom screen, echocardiogram, periodic colonoscopy, and annual LFTs, BMP and UA.
3. Due to the bimodal distribution in age at presentation, adult providers may directly encounter teenagers and young adults with primary genitourinary rhabdomyosarcoma.
4. Follow-up guidelines should be based on prior treatment received and mirror the indications above for Wilms tumor, however, late pelvic effects are more substantial in this population, including:
   (a) Infertility
   (b) Bladder dysfunction
   (c) Sexual dysfunction
   (d) Rectal/fecal dysfunction
5. All patients with a history of pelvic surgical and/or radiotherapy should be monitored at least annually for all four of the areas listed above and for those who have undergone urinary diversion, routine surveillance guidelines for B12, renal function, incontinence, stones, and cancer should be followed.

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