CONGENITAL LIFELONG UROLOGY:

CARING FOR THE ADOLESCENT AND ADULT PATIENT WITH CONGENITAL AND CHILDHOOD GU CONDITIONS

EDITORS: DAN WOOD AND HADLEY M. WOOD

A Joint SIU-ICUD International Consultation

Seoul, South Korea, October 4-7, 2018

Co-sponsored by
SIU (Société Internationale d'Urologie)
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Abbreviations Used in the Text

ABBREVIATION	FULL TERM
5-ARI	5α-reductase inhibitor
AAP	American Academy of Pediatrics
AB	α-blocker
AC	augmentation cystoplasty
ACE	angiotensin-converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ADPKD	autosomal dominant polycystic kidney disease
AKI	acute kidney injury
ARB	angiotensin receptor blocker
ARM	anorectal malformation
ART	assisted reproductive technology
AUA	American Urological Association
AYA	adolescent and young adult
BE	bladder exstrophy
BEEC	bladder exstrophy-epispadias complex
BHP	benign prostatic hyperplasia
BNR	bladder neck reconstruction
BUN	blood urea nitrogen
CAH	congenital adrenal hyperplasia
CAKUT	congenital anomalies of the kidney and urinary tract
CASV	congenital absence of seminal vesicles
CAT	computerized axial tomography
CAVD	congenital absence of the vas deferens
CBAVD	congenital bilateral absence of the vas deferens
CBE	classic bladder exstrophy
CCC	continent catheterizable channel
CE	cloacal exstrophy
CF	cystic fibrosis

ABBREVIATION	FULL TERM
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
CIC	clean intermittent catheterization
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD-EPI-Cr	Chronic Kidney Disease Epidemiology Collaboration creatinine
CKD-EPI-CysC	Chronic Kidney Disease Epidemiology Collaboration cystatin C
CKiD	Chronic Kidney Disease in Children study
COPUM	congenital obstructing posterior urethral membrane
Cr	creatinine
CT	computed tomography
CUAVD	congenital unilateral absence of the vas deferens
CysC	cystatin C
DLPP	detrusor leak point pressure
DMSA	dimercaptosuccinic acid
DSD	differences of sexual development
DTPA	diethylenetriaminepentaacetic acid
Dx/HA	dextranomer/hyaluronic acid
E. coli	*Escherichia coli*
EAU	European Association of Urology
ED	erectile dysfunction
EDTA	ethylenediaminetetraacetic acid
eGFR	estimated glomerular filtration rate
ESPU	European Society for Paediatric Urology
ESRD	end-stage renal disease
ESWL	extracorporeal shock wave lithotripsy
EUROCAT	European Surveillance of Congenital Anomalies
FSH	follicle-stimulating hormone
FURS	flexible ureteroscopy
GFR	glomerular filtration rate
GMS	glans-urethral meatus-shaft

ABBREVIATION	FULL TERM
GOR	grade of recommendation
GU	genitourinary
HOPE	Hypospadias Objective Penile Evaluation
HOSE	Hypospadias Objective Scoring Evaluation
HR	hazard ratio
ICCS	International Children's Continence Society
ICSI	intracytoplasmic sperm injection
ItalKid	Italian Pediatric Registry of Renal Failure
IUI	intrauterine insemination
IVF	in vitro fertilization
KDIGO	Kidney Disease: Improving Global Outcomes
KFRE	kidney failure risk equation
KS	Klinefelter's syndrome
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
LOE	level of evidence
LUT	lower urinary tract
LUTD	lower urinary tract disease
LUTS	lower urinary tract symptom
MACE	Malone antegrade continence enema
MAG-3	mercaptoacetyltriglycine-3
max	maximum
MCUG	micturating cystourethrogram
MDR	multidrug resistant
MDRD	modification of diet in renal disease
MESA	microsurgical epididymal sperm aspiration
min	minimum
MIS	müllerian inhibiting substance
MMC	myelomeningocele
mpMRI	multiparametric magnetic resonance imaging
MPUH	Muljibhai Patel Urological Hospital
MRI	magnetic resonance imaging
MRKH	Mayer-Rokitansky-Küster-Hauser syndrome

ABBREVIATION	FULL TERM
MS	multiple sclerosis
mTESE	microdissection testicular sperm extraction
N/A	not applicable
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies
NBD	neuropathic bladder dysfunction
NGB	neurogenic bladder
NSF	nephrogenic systemic fibrosis
NTD	neural tube defect
NU	not urologic
OAB	overactive bladder
OEIS	omphalocele, exstrophy, imperforate anus, and spinal defects
OR	odds ratio
PBS	prune belly syndrome
PCNL	percutaneous nephrolithotomy
PDMS	polydimethylsiloxane
PESA	percutaneous epididymal sperm aspiration
PFMT	pelvic-floor muscle training
POP	pelvic organ prolapse
POP-Q	Pelvic Organ Prolapse quantification
PSA	prostate-specific antigen
PTH	parathyroid hormone
PUV	posterior urethral valve
PVR	postvoid residual
PVS	penile vibratory stimulation
RCT	randomized controlled trial
Q_{max}	maximum flow rate
QoL	quality of life
SB	spina bifida
SCI	spinal cord injury
SCOS	Sertoli-cell–only syndrome
SFU	Society for Fetal Urology

ABBREVIATION	FULL TERM
SPA	suprapubic aspiration
TIP	tubularized incised plate
TMP-SMZ	trimethoprim-sulfamethoxazole
TOMAX	TO MAX-imize sensation, sexuality, and quality of life procedure
TRAQ	Transition Readiness Assessment Questionnaire
UDS	urodynamic study
UDT	undescended testes
UP	urethral plate
UPJ	ureteropelvic junction
UTD	Urinary Tract Dilatation
UTI	urinary tract infection
VACTERL	vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities
VC	ventral curvature
VCMG	video cystometrogram
VUDS	video urodynamics
VUR	vesicoureteral reflux
YAG	yttrium aluminum garnet

Letter from the Chairman

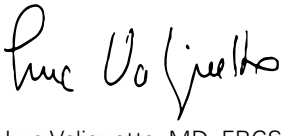
Luc Valiquette
Canada

It is an exciting time in the ever-evolving practice of urology. As Chair of the International Consultation of Urological Diseases, it is my privilege to present this publication that pulls together expertise in transitional urology from across the globe. This is the 16th annual Joint Consultation of the Société Internationale d'Urologie (SIU) and the International Consultation on Urological Diseases (ICUD), a collaborative initiative that seeks to address timely, critical needs for urological care worldwide.

This year, the Joint Consultation focused on the most salient issues that arise when patients with congenital urological disease transition from pediatric care to adult care. The aim of this Consultation is to propose innovative, actionable consensus statements leveraging clinical expertise and evidence-based medicine. This publication provides original conclusions, bridging the gap between pediatric and adult care skillsets for the improvement of the management of adult patients with congenital urological disorders.

The *SIU-ICUD Joint Consultation on Congenital Lifelong Urology* brought together a large international faculty with urology expertise across both pediatric and adult care. These experts were subsequently organized into six unique committees, which met at the 2018 SIU Congress in Seoul, Korea. Each committee produced a chapter in this book on an important topic in transitional urology. The resulting consensus statements were further reviewed by the Consultation Scientific Committee, comprised of the two Chairs of the Consultation, together with the Chairs from each unique committee.

This expert Joint Consultation on transitional care is unparalleled. I would like to thank the Consultation Chairs, Hadley Wood and Dan Wood, for their leadership and dedication, as well as the members of the six committees who contributed to the publication. This enthusiastic collaboration resulted in a truly global consultation, providing innovative consensus statements to address important unmet needs in urological care. It is my sincere hope that this publication will be used often as a reference guide for urologists worldwide to help patients in their transition from pediatric care to adult care.



Luc Valiquette, MD, FRCSC, FACS
Chairman, International Consultation on Urological Diseases

Preface

Dan Wood
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Hadley M. Wood
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In 2018 the Société Internationale d'Urologie-International Consultation on Urological Diseases (SIU-ICUD) presented a unique opportunity for the first joint Consultation examining Congenital Lifelong Urology. This represents a landmark interdisciplinary and international effort to fulfill the promise made in pediatric life for our adult patients affected by congenital diseases. Unlike prior ICUDs, data acquisition in the field has been limited by a prior lack of instruments to standardize the wide range of disease entities captured by this umbrella and the developing treatments offered over the years. Likewise, high-quality long-term studies on patients treated in pediatric life are logistically difficult and costly to execute. Our committee chairs and authors have made great efforts to highlight critical aspects of this field and identify when possible best practices and opportunities for further investigation.

Chapter 1 (Misseri *et al.*) reviews the current state of understanding around the process of transitioning children into adult care models. There are many factors that influence the success of transition to adult care. Patient and family preferences and experiences, provider bias and availability, cultural expectations, systemic limitations (e.g., insurance and payment structures and physical facilities) are just a handful of variables that drive patients towards successful transition of care or keep them engaged in healthcare as they move between pediatric and adult care. The complexity of this process exemplifies the need for a team approach to patients with medically and surgically complex disease; the make-up of these teams will vary by region and availability as well as individual patient's medical needs.

Chapter 2 reviews (Wiener *et al.*) reviews the pediatric approach to many congenital issues requiring lifelong care. This allows providers to understand what requirements will need to be in place when "receiving" such patients into adult healthcare. In pediatric life, preservation of renal function, avoidance of infections and achieving continence are, rightly, primary aims. A special focus on complex bladder reconstruction is provided (with a continuation of that discussion in Chapter 4) focusing on long-term outcomes and the treatment of complications.

Chapter 3 (De Win *et al.*) focusses specifically on aspects of genitoplasty, including cosmesis, fertility, and psychosocial outcomes. Particularly in light of recent trends towards delayed elective genitoplasty in childhood, many such issues become relevant around the time of sexual maturity. For example, chordee associated with hypospadias repair is discussed, as well as re-assessment and treatment considerations in peri-adolescent life or young adulthood. For rare diseases (e.g. vaginal agenesis) or diagnoses with widely variable and heterogeneous phenotypic presentations (e.g. differences of sexual development) we are unable to provide much more than expert opinion as data are substantially limited.

As mentioned, Chapter 4 (Kielb et al.) develops the discussion from Chapter 2 on complex bladder reconstruction. Chapter 4 addresses specific adult-onset conditions such as pelvic organ prolapse which may be influenced by both the disease state (e.g. bladder exstrophy) and the adaptive behaviors some affected individuals must adopt for self-care (e.g. Valsalva voiding). Additionally, adult specific conditions such as pregnancy and female fertility management are discussed within the context of previously reconstructed patients.

Chapter 5 (Yerkes *et al.*) examines the importance of the upper tracts, focusing first on our existing armamentarium of surveillance options, expected natural history including metabolic challenges and the role of nephrologists in shared care across the lifespan. Urological issues specific to advanced CKD and ESRD are addressed, in particular polyuria associated with valve kidneys, preparation of a low pressure urinary reservoir for renal transplantation and the management of defunctionalized or remnant urological structures after progression to renal replacement therapy. The last section of this chapter reviews special aspects of nephrolithiasis management in patients with congenitally anomalous kidneys.

Finally, Chapter 6 (Taylor *et al.*) provides a particular focus on acquired age-related urological conditions within the context of urological systems that have been adapted iatrogenically, behaviorally and congenitally over the years. The purpose of this chapter is to specifically focus on "routine" urological considerations, like prostate cancer surveillance, in populations with atypical physiology and anatomy.

We hope you find this work useful and relevant to your working practice and will be forgiving about our inability to be wholly inclusive of every diagnosis or treatment impact herein. This issue is the first international consultation of its kind and represents the culmination of hundreds of hours of thought and work coupled with decades of experience by the authors and the SIU editorial team for which the editors are forever grateful. We hope this work provides readers with improved information and additional confidence in delivering on the promise made to parents when their children were born about the need for lifelong care, of their children, by the urological community.

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Evidence-Based Medicine Overview of the Main Steps for Developing and Grading Guideline Recommendations

P. Abrams, S. Khoury, A. Grant

Introduction

The International Consultation on Urological Diseases (ICUD) is a non-governmental organization registered with the World Health Organisation (WHO). In the last ten years, consultations have been organized on BPH, prostate cancer, urinary stone disease, nosocomial infections, erectile dysfunction and urinary incontinence. These consultations have looked at published evidence and produced recommendations at four levels: highly recommended, recommended, optional and not recommended. This method has been useful but the ICUD believes that there should be more explicit statements of the levels of evidence that generate the subsequent grades of recommendations.

The Agency for Health Care Policy and Research (AHCPR) have used specified evidence levels to justify recommendations for the investigation and treatment of a variety of conditions. The Oxford Centre for Evidence-Based Medicine have produced a widely accepted adaptation of the work of AHCPR. (June 5th 2001, www.cebm.net).

The ICUD has examined the Oxford guidelines and discussed with the Oxford group their applicability to the consultations organized by ICUD. It is highly desirable that the recommendations made by the consultations follow an accepted grading system supported by explicit levels of evidence.

The ICUD proposes that future consultations should use a modified version of the Oxford system which can be directly "mapped" onto the Oxford system.

1. First Step

Define the specific questions or statements that the recommendations are supposed to address.

2. Second Step

Analyze and rate (level of evidence) the relevant papers published in the literature.

The analysis of the literature is an important step in preparing recommendations and their guarantee of quality.

2.1 What papers should be included in the analysis?

- Papers published, or accepted for publication in the peer-reviewed issues of journals.
- The committee should do its best to search for papers accepted for publication by the peer-reviewed journals in the relevant field but not yet published.
- Abstracts published in peer-reviewed journals should be identified. If of sufficient interest, the author(s) should be asked for full details of methodology and results. The relevant committee members can then "peer review" the data, and if the data confirms the details in the abstract, then that abstract may be included, with an explanatory footnote. This is a complex issue – it may actually increase publication bias as "uninteresting" abstracts commonly do not progress to full publication.
- Papers published in non-peer-reviewed supplements will not be included. An exhaustive list should be obtained through:
  - I. The major databases covering the last ten years (e.g. Medline, Embase, Cochrane Library, Biosis, Science Citation Index).
  - II. The table of contents of the major journals of urology and other relevant journals, for the last three months, to take into account the possible delay in the indexation of the published papers in the databases.

It is expected that the highly experienced and expert committee members provide additional assurance that no important study would be missed using this review process.

2.2 How are papers analyzed?

Papers published in peer-reviewed journals have differing quality and level of evidence. Each committee will rate the included papers according to levels of evidence (see below).

The level (strength) of evidence provided by an individual study depends on the ability of the study design to minimize the possibility of bias and to maximize attribution.

It is influenced by:

The type of study, whose hierarchy is outlined below:

- Systematic reviews and meta-analysis of randomized controlled trials
- Randomized controlled trials
- Non-randomized cohort studies
- Case-control studies
- Case series
- Expert opinion

How well the study was designed and carried out

Failure to give due attention to key aspects of study methodology increases the risk of bias or confounding factors, and thus reduces the study's reliability.

The use of **standard checklists** is recommended to insure that all relevant aspects are considered and that a consistent approach is used in the methodological assessment of the evidence.

The objective of the checklist is to give a quality rating for individual studies.

How well the study was reported

The ICUD has adopted the CONSORT statement and its widely accepted checklist. The CONSORT statement and the checklist are available at www.consort-statement.org.

2.3 How are papers rated?

Papers are rated following a level of evidence scale.

ICUD has modified the Oxford Centre for Evidence-Based Medicine levels of evidence.

The levels of evidence scales vary between types of studies (i.e. therapy, diagnosis, differential diagnosis/ symptom prevalence study) the Oxford Centre for Evidence-Based Medicine Website: www.cebm.net.

3. Third Step: Synthesis of the Evidence

After the selection of the papers and the rating of the level of evidence of each study, the next step is to compile a summary of the individual studies and the overall direction of the evidence in an **Evidence Table**.

4. Fourth Step: Considered Judgment (Integration of Individual Clinical Expertise)

Having completed a rigorous and objective synthesis of the evidence base, the committee must then make a judgment as to the grade of the recommendation on the basis of this evidence. This requires the exercise of judgment based on clinical experience as well as knowledge of the evidence and the methods used to generate it. Evidence-based medicine requires the integration of individual clinical expertise with the best available external clinical evidence from systematic research. Without the former, practice quickly becomes tyrannized by evidence, for even excellent external evidence may be inapplicable to, or inappropriate for, an individual patient. On the other hand, without current best evidence, practice quickly becomes out of date. Although it is not practical to lay our "rules" for exercising judgment, guideline development groups are asked to consider the evidence in terms of quantity, quality, and consistency, as well as applicability, generalizability and clinical impact.

5. Fifth Step: Final Grading

The grading of the recommendation is intended to strike an appropriate balance between incorporating the complexity of type and quality of the evidence, and maintaining clarity for guideline users.

The recommendations for grading follow the Oxford Centre for Evidence-Based Medicine. The levels of evidence shown below have again been modified in the light of previous consultations. There are now four levels of evidence instead of five.

The grades of recommendation have not been reduced and a "no recommendation possible" grade has been added.

6. Levels of Evidence and Grades of Recommendation for Therapeutic Interventions

All interventions should be judged by the body of evidence for their efficacy, tolerability, safety, clinical effectiveness and cost-effectiveness. It is accepted that, at present, little data exists on cost-effectiveness for most interventions.

6.1 Levels of evidence

Firstly, it should be stated that any level of evidence may be positive (the therapy works) or negative (the therapy doesn't work). A level of evidence is given to each individual study.

Level of Evidence	Criteria
I	▪ Incorporates Oxford 1a, 1b ▪ Usually involves: ▪ meta-analysis of trials (randomized controlled trials [RCTs]) or, ▪ a good-quality RCT or, ▪ "all or none" studies in which treatment is not an option (e.g. in vesicovaginal fistula)
II	▪ Incorporates Oxford 2a, 2b and 2c ▪ Includes: ▪ ***low-quality RCT*** (e.g. <80% follow-up), ▪ ***meta-analysis*** (with homogeneity) of ***good-quality prospective cohort studies*** ▪ May include a single group when individuals who develop the condition are compared with others from within the original cohort group. ▪ There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group
III	▪ Incorporates Oxford 3a, 3b and 4 ▪ Includes: ▪ ***good-quality retrospective case-control studies***, where a group of patients who have a condition are matched appropriately (e.g. for age, sex, etc.) with control individuals who do not have the condition ▪ ***good-quality case series,*** where a complete group of patients, all with the same condition, disease or therapeutic intervention, are described without a comparison control group
IV	▪ Incorporates Oxford 4 ▪ Includes ***expert opinion***, where the opinion is based not on evidence but on "first principles" (e.g. physiological or anatomical) or bench research. ▪ The ***Delphi process*** can be used to give expert opinion greater authority: ▪ involves a series of questions posed to a panel ▪ answers are collected into a series of "options" ▪ these "options" are serially ranked; if a 75% agreement is reached, then a Delphi consensus statement can be made

6.2 Grades of recommendation

The ICUD will use the four grades from the Oxford system. As with levels of evidence, the grades of evidence may apply either positively (procedure is recommended) or negatively (procedure is not recommended). Where there is disparity of evidence, for example if there were three well-conducted RCTs indicating that Drug A was superior to placebo, but one RCT whose results show no difference, then there has to be an individual judgment as to the grade of recommendation given and the rationale explained.

Grade A recommendation usually depends on consistent level I evidence and often means that the recommendation is effectively mandatory and placed within a clinical-care pathway. However, there will be occasions where excellent evidence (level I) does not lead to a Grade A recommendation, for example, if the therapy is prohibitively expensive, dangerous or unethical. Grade A recommendation can follow from Level II evidence. However, a Grade A recommendation needs a greater body of evidence if based on anything except Level I evidence.

Grade B recommendation usually depends on consistent level 2/3 studies, or "majority evidence" from RCTs.

Grade C recommendation usually depends on level 4 studies or "majority evidence" from level 2/3 studies or Delphi processed expert opinion.

Grade D "No recommendation possible" would be used where the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process, such as by Delphi.

7. Levels of Evidence and Grades of Recommendation for Methods of Assessment and Investigation

From initial discussions with the Oxford group, it is clear that application of levels of evidence/grades of recommendation for diagnostic techniques is much more complex than for interventions. The ICUD recommends that, as a minimum, any test should be subjected to three questions:

1. Does the test have good technical performance? For example, do three aliquots of the same urine sample give the same result when subjected to dipstick testing?
2. Does the test have good diagnostic performance, ideally against a "gold standard" measure?
3. Does the test have good therapeutic performance, that is, does the use of the test alter clinical management? Does the use of the test improve outcome?

For the third component (therapeutic performance) the same approach can be used as for section 6.

8. Levels of Evidence and Grades of Recommendation for Basic Science and Epidemiology Studies

The proposed ICUD system does not easily fit into these areas of science. Further research needs to be carried out in order to develop explicit levels of evidence that can lead to recommendations as to the soundness of data in these important aspects of medicine.

Conclusion

The ICUD believes that its consultations should follow the ICUD system of levels of evidence and grades of recommendation, where possible. This system can be mapped to the Oxford system.

There are aspects to the ICUD system that require further research and development, particularly diagnostic performance and cost-effectiveness, and also factors such as patient preference.

Summary of the International Consultation on Urological Disease Modified Oxford Centre for Evidence-Based Medicine Grading System for Guideline Recommendations

Levels of Evidence	Description
I	Meta-analysis of RCTs or high-quality RCT
II	Low-quality RCT or good-quality prospective cohort study
III	Good-quality retrospective case-control study or cohort study
IV	Expert opinion

Abbreviation: RCT=randomized controlled trial

Summary of the International Consultation on Urological Disease Modified Oxford Centre for Evidence-Based Medicine Grading System for Guideline Recommendations

Grades of Recommendation	Description
A	Usually consistent with level I evidence
B	Consistent level II or III evidence or "majority evidence" from RCTs
C	Level IV evidence or "majority evidence" from level II or III studies
D	No recommendation possible because of inadequate or conflicting evidence

RCT=randomized controlled trial

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The Basics of Transition

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The Basics of Transition

1.1 Conditions Requiring Transition

Improvements in treatment have led to a marked increase in survival of children with congenital diseases over recent decades. Transition to adult-centred care is emerging as a priority across all chronic pediatric conditions. Adolescence and young adulthood are times of physical, psychological, and social change. Individuals with special health care needs face additional challenges as they manage their chronic diseases during this time. The process of transitioning to adult services has been shown to be associated with health deterioration for diabetes mellitus[1-4] and congenital heart disease.[5,6] In a 2007 survey in the United States, this decline in health care status was partially associated with decreased access to care.[7] The goal of the transition process is to maximize lifelong functioning and potential through uninterrupted healthcare services as the individual progresses from adolescence to adulthood.[8]

Within the specialty of urology, many children will require continued urologic monitoring and/or treatment into adulthood. The genitourinary tract is frequently affected by major birth defects. In addition, congenital abnormalities of the central nervous system often secondarily impair bladder and genital function. Furthermore, interventions for these congenital conditions in childhood are known to present long-term urologic consequences. The urologic goals for these individuals as they progress through the life span are to:

- Preserve kidney function
- Optimize lower urinary function and manage urinary incontinence
- Minimize complications from prior procedures and have access to surgical intervention, if necessary
- Have appropriate monitoring for associated malignancy
- Be prepared for the sexual and reproductive aspects of adult life, and
- Have the patient assume responsibility for their own health care maintenance and decision-making, if they are developmentally and cognitively able to do so

Congenital conditions requiring transition to adult care comprise a diverse set of disorders that can have long-term urologic sequelae. Several recent publications, including those from the International Children's Continence Society and from the International Consultation on Urological Diseases, have enumerated urologic disorders that require adult care.[9-12] **Table 1-1** lists some of these disorders.

TABLE 1-1 Childhood Urologic Conditions With Potential for Long-Term Urologic Adverse Outcomes

	Renal function	Lower urinary tract function	Urologic malignancy risk	Sexual/ reproductive function
Posterior urethral valves	x	x		x
Exstrophy-epispadias	x	x	x	x
Vesicoureteral reflux	x	x		x
Prune belly	x	x	x	x
Myelomeningocele	x	x	x	x
Hypospadias		x		x
Differences of sex development		x	x	x
Cloacal malformation	x	x	x	x
Undescended testicle			x	x

Less complicated urologic diseases of childhood can also have lasting effects, but not all these disorders will require regular follow-up with an adult-urology specialist. Optimal follow-up can sometimes be difficult to define. For example, a unilateral undescended testicle corrected before puberty does not show difference in paternity compared with controls,[13] but there is still increased risk of malignancy. For women with childhood vesicoureteral reflux, the presence of renal scarring is associated with gestational hypertension and pre-eclampsia during pregnancy.[14,15] Distal hypospadias complications may arise in adulthood, although the risks and costs of ongoing surveillance through childhood are considerable.[16]

Acquired conditions in childhood, such as spinal cord injury and bladder dysfunction from behavioural disorders and substance abuse, may also necessitate lifelong urology care. More attention to urologic issues in the pediatric cancer survivorship literature is also emerging. Survivors of childhood cancer have an excess risk of urologic diseases and reproductive challenges that often remains elevated throughout life.[17] Young men who have survived childhood cancer are more likely to have problems with erectile dysfunction, hypogonadism, and infertility.[18-20] Individuals who need lifelong urology services will likely increase as we continue to learn more about the long-term effects of pediatric diseases and interventions.

1.1.1 Kidney function

Renal preservation is the primary treatment goal in childhood urinary tract disorders. This goal remains throughout life. Having a well-established transition process is particularly important for renal function preservation, as renal deterioration can be silent and therefore may not trigger a patient to present themselves. Renal failure may be inevitable for some disease processes. Conversely, renal failure may result directly as a consequence of poorly managed bladder dysfunction, recurrent obstruction, stones, or urinary tract infections (UTIs).

Many individuals with congenital urologic disorders will be at risk for renal deterioration. In individuals with posterior urethral valves, kidneys are likely to have already sustained damage by birth. Very few infants will have a normal renal ultrasound at presentation.[21] One-third or more will progress to end-stage renal disease.[22-24] This progression may be an inevitable consequence of the underlying condition. In contrast, with myelomeningocele, kidneys are overwhelmingly normal on renal ultrasound at birth.[25] Studies have suggested that optimal management of bladder dysfunction can preserve renal function.[25,26] Nevertheless, chronic kidney disease is higher in adults with myelomeningocele compared to the general population.[27,28]

In those who are vulnerable, renal function often deteriorates during puberty and young adulthood, the period of time when patients are at greatest risk of being lost to medical care due to unsuccessful transition. In a series of children with glomerular filtration rate <70 mL/min/1.73 m^2 from vesicoureteral reflux or posterior urethral valves, 43% began to have deterioration of renal function after puberty.[29] In these individuals at risk of renal deterioration, surveillance with renal ultrasound, identification of proteinuria, surveillance of blood pressure, and assessment of renal function are recommended. If there is renal deterioration or worsening hydronephrosis, obstruction should be excluded. In the absence of obstruction, proteinuria is an important early warning sign; other causes like recurrent UTIs should be considered.[9,12] Early intervention with angiotensin-converting enzyme inhibitors and strict blood pressure control will not prevent end-stage renal failure but may delay progression of renal disease.[30] Appropriate management of these individuals requires collaboration between urologists and nephrologists.

1.1.2 Lower urinary tract function

For the adult patient with congenital urologic disease, lower urinary tract function may not have been appropriately addressed in childhood or may deteriorate with time. Continued assessment of lower urinary tract function remains important, as worsening symptoms may adversely affect quality of life and renal function. Worsening lower urinary tract function in a young adult with myelomeningocele may represent a deterioration in their underlying condition, eg, tethered cord. Worsening lower urinary tract function in a young man with posterior urethral valves may represent decreased concentrating ability of the kidneys.

Lower urinary tract function often changes in adolescence or early adulthood in individuals with congenital urologic diseases. In posterior urethral valves, postpubertal bladders tend to have decreased detrusor overactivity, decreased sustained contractility, and overdistention.[31] In individuals with myelomeningocele, total cystometric bladder capacity and detrusor leak point pressure increased with puberty.[32] Both of these situations may result in incomplete emptying, urinary infections, urinary incontinence, or deterioration in renal function.

Lower urinary tract symptoms are common in adults with congenital urologic disorders. Men with corrected hypospadias reported lower urinary tract symptoms twice as often as controls and were less satisfied with their urinary function. Spraying, postvoid dribbling, and a feeling of incomplete emptying were prevalent.[33] Although many individuals with congenital urologic disorders are able

to achieve urinary continence, recent reports document the continued prevalence of urinary incontinence in adults with posterior urethral valves,[34] exstrophy,[35,36] myelomeningocele,[37] congenital adrenal hyperplasia (CAH),[38,39] and cloacal abnormalities.[40,41] For adults with myelomeningocele[42] and women with exstrophy,[35] decreased quality of life associated with urinary incontinence has been demonstrated.

1.1.2.1 Recommendation for lower urinary tract function

- Any change to urologic function (eg, worsened incontinence, escalating infections, stones, new hydronephrosis) that occurs during periadolescence merits a thorough investigation, including a detailed history and appropriate diagnostic testing.

1.1.3 Long-term surgical complications

Surgical treatment in childhood can also create additional needs for long-term monitoring. Children with bladder dysfunction from myelomeningocele, exstrophy, and posterior urethral valves will often proceed to augmentation cystoplasty or urinary diversion after failure of initial management. In a snapshot of an adult myelomeningocele clinic with a median age of 30 years, 15% had previously undergone augmentation cystoplasty.[43]

Augmentation cystoplasty can create metabolic disturbances. Urine contact with intestinal epithelium allows an increase in exchange of bicarbonate for chloride ions, causing a hyperchloremic metabolic acidosis. The severity of this complication depends on length of bowel used, bladder management habits, and baseline renal function. More severe disturbances may require treatment with potassium citrate or sodium bicarbonate, a change in bladder management, or incontinent diversion.[44]

The risk of vitamin B12 deficiency increases over time in patients who undergo ileal augmentation cystoplasty.[45,46] The absorption of oral vitamin B12 depends on an intact exocrine pancreas to signal the stomach to synthesize intrinsic factor. The bound complex of intrinsic factor B12 is absorbed in the terminal ileum. Despite surgical preservation of at least 15 cm of distal ileum during the augmentation cystoplasty, vitamin B12 deficiency can occur; the consequences of not detecting this is an irreversible neuropathy. Therefore, regular monitoring is important.

More that one-third of patients will require further or revision surgery following augmentation cystoplasty. In a decade-long retrospective review, the indications for reoperation included bowel obstruction, bladder stones, and bladder perforation.[47] About 75% of children undergoing augmentation cystoplasty will have a continent catheterizable channel created.[44] The risk of stomal complications continues over the channel's lifetime.[48] Often, these individuals will undergo procedures as non-obese children. The onset of obesity in adolescence and adulthood is strongly associated with channel complications.[44]

Bladder stones are often observed following augmentation cystoplasty.[49,50] In bladder augmentation with a continent abdominal stoma, there is a 50% incidence of bladder stone formation within 5 years of surgery. Half of those patients will have bladder stone recurrence within 5 years of their first stone.[44]

Spontaneous perforation of the augmented bladder is a life-threatening complication of augmentation cystoplasty. Patients may present as very ill-appearing, with abdominal pain and fever. However, because many who have undergone augmentation cystoplasty have decreased abdominal sensation, atypical presentations can occur and may delay diagnosis unless a high index of suspicion is maintained. The incidence of spontaneous perforation is about 3% to 4%.[44,51,52] In adults, spontaneous perforation was primarily correlated with substance abuse and noncompliance with intermittent catheterization.[53] Individuals transitioning from pediatric to adult-centred care without the foundation of knowledge to maintain their own health are particularly at risk.

1.1.4 Malignancy

Increased risk of malignancy also accompanies many congenital urologic diseases. The most well-known association is between cryptorchidism and testicular cancer, with a 2.75 to 8 relative risk.[54] In males affected with prune belly syndrome, cryptorchidism is virtually universal, and testicular tumours have been reported.[55-57]

The risk of malignant germ cell tumours is also elevated in many conditions classified as differences of sex development. This risk varies among this diverse set of disorders. The risk of malignancy depends on several factors, including the presence of a defined gonadoblastoma region on the Y chromosome, the position of the gonad, and other microenvironmental factors. Optimal management of the gonad balances the malignancy risk with fertility and endocrine potential.[58] The highest risk of malignancy is in those with testis-specific protein Y encoded gonadal dysgenesis and partial androgen insensitivity syndrome with intra-abdominal gonads.[59]

Colorectal cancer risk is increased by 100-fold after ureterosigmoidostomy and its variations, such as the Mainz pouch II and Mansoura rectal bladder, which allow urine and feces to be mixed.[60] Unless the diversion has been revised and the ureterocolic anastomosis has been excised, these individuals require annual surveillance sigmoidoscopy once the diversion has been in place for 10 years.[61]

Individuals with bladder exstrophy[62] and myelomeningocele[63] are at increased risk for bladder cancer. A recent case-control study showed that this increased risk is independent of presence of a bowel segment in the bladder (as with augmentation cystoplasty).[64] In patients with congenital bladder dysfunction who develop cancer, age at presentation is younger and cancer stage is higher compared to bladder cancer in the general population. These individuals often present with gross hematuria coupled with UTI; suprapubic, abdominal, or perineal pain; or difficulty catheterizing. Presentation with a change in symptoms necessitates urgent imaging and endoscopy; routine screening for malignancy in this population has not been shown to be effective.[65]

Cancer of the neovagina created for congenital anomalies has also been documented. Histological type is dependent on the graft material, with squamous cell carcinoma developing in split-thickness skin graft or McIndoe variations and adenocarcinoma developing in intestinal grafts. Again, age at presentation is younger compared to vaginal cancer in the general population. Presenting symptoms are bloody or clear vaginal discharge or postcoital bleeding. No specific surveillance strategies beyond regular pelvic exams are recommended.[66]

1.1.5 Sexual/reproductive function

Sexual activity is an important aspect of adulthood. However, initiation of sexual behaviour can be associated with preventable consequences, including risk of sexual abuse, sexually transmissible diseases, and unwanted pregnancy.[67,68] Therefore, those looking after affected young adults need to be proactive in initiating conversations about sex and educating patients where necessary. Individuals with congenital urologic disorders may also have additional concerns related to their diagnoses. Ideal sex education should address self-esteem and body image, public and private body parts, emotional and physical changes of puberty, menstruation, physical mechanics of sex and reproduction, sexually transmissible infections, appropriate and inappropriate expressions of sexuality, safer sex, and birth control.[69] In the myelomeningocele population, many individuals felt that they had received little or no sexual education related to their disability.[70-72]

In individuals with congenital anomalies of the genitalia, postpubertal anatomy can potentially affect or limit sexual and reproductive function. There is ongoing dialogue regarding the timing of surgical intervention for those with congenital anomalies of the genitalia, particularly in differences of sex development.[73,74] There is currently little long-term data regarding patients not undergoing genital reconstruction in childhood. Whether or not patients have undergone surgery, postpubertal assessment of genital function allows individuals to be informed about treatment options.

One of the surgical goals for penile reconstructive surgery in congenital urologic disorders is to create a straight penis sufficient for sexual penetrative intercourse. With hypospadias, dissatisfaction with phallic appearance is reported in 20% to 30% of patients and is most commonly related to concerns about penile size and residual chordee.[11] Similarly, in adult men with exstrophy, penile size and dorsal chordee were reasons given for unsatisfactory sexual intercourse.[75,76] Results of childhood penile reconstruction should be reassessed after the period of rapid penile growth at puberty. New onset curvature may occur, and revision surgery may be needed in adolescence and young adulthood.

Recent studies have used the International Index of Erectile Function to evaluate erectile function in men with congenital urologic disorders. In two recent studies of adult men with corrected hypospadias, the majority of men had normal erectile function and none had severe dysfunction.[77,78] However, some select groups may be more likely to have erectile problems. In a series of adults with hypospadias presenting for redo urethroplasty, more than half reported some erectile dysfunction, with 28% having severe dysfunction.[79] Similarly, although on average adult men with exstrophy[80-82] and myelomeningocele[83] report mild to moderate dysfunction, the level of dysfunction varies widely from study to study. Individual studies in adult men with exstrophy have reported no dysfunction in 93%,[84] while others have reported severe dysfunction in about 25%.[36] More than 75% of adult men with myelomeningocele have erectile dysfunction that is related to difficulty in maintaining erections.[85]

Ejaculatory dysfunction is also prevalent in adult men with congenital urologic disorders. In hypospadias, ejaculatory dysfunction—including reduced propulsion, spraying, and anejaculation—is reported in up to 37% of adult men.[11] Multiple reports of adult men with exstrophy report ejaculatory dysfunction. Less than one-quarter of men with exstrophy had antegrade ejaculation, which

was often characterized as weak or dribbling.[82,84] In myelomeningocele, particularly with lower-level lesions, ejaculation is preserved. However, although antegrade ejaculation occurs in 53% to 88% of men with myelomeningocele, it is often described as dribbling and not associated with orgasm.[86]

In men with exstrophy[82,84] and myelomeningocele,[87] even when semen is obtainable, it is often of poor quality. Paternity for individuals with these congenital urologic disorders has been reported both with and without assisted reproductive technology.

Female postpubertal anatomy can also limit sexual and reproductive function. Young women with cloacal anomaly and differences of sex development may undergo vaginal reconstruction with goals of creating a patent conduit for menstrual flow and a vagina for sexual intercourse. Women with cloacal anomalies have a high incidence of müllerian abnormalities that may only become symptomatic after puberty. Modes of presentation may include with primary amenorrhea (due to either müllerian agenesis or obstruction) or cyclical abdominal pain. Müllerian duplication is common, and the smaller, obstructed side may go undetected until puberty.[40,88] One-third of patients with a functional uterus require additional procedures to relieve obstruction of menstrual flow.[89] Vaginal stenosis is common after vaginoplasty, and the majority of patients require repeat operations, in adolescence or adulthood, to achieve a patent vagina for sexual intercourse.[90-92]

Pelvic organ prolapse is common in adult women with congenital urologic disorders, including myelomeningocele[93,94] and bladder exstrophy.[93,95,96] These young women present with pelvic organ prolapse at a younger age and more advanced stage.[93] Between 30% and 50% of women with bladder exstrophy will develop prolapse at a mean age of 16 years old. Many will require revision genitoplasty and prolapse repair for sexual function.[97]

Recently, female sexual function has been assessed in these individuals with validated questionnaires. The most commonly used is the Female Sexual Function Index, which evaluates domains of desire, arousal, lubrication, orgasm, satisfaction, and pain. Overall, female exstrophy patients were found to have good sexual function. In one study, self-reported sexual function was normal in 69%, with the remaining 31% described as being at risk for sexual dysfunction.[96] In another study, sexual dysfunction for adult women with bladder exstrophy was not lower than controls.[98] Interestingly, one study found that urinary diversion was associated with improved sexual function scores.[99] For women with CAH who had undergone feminizing genitoplasty, published results are variable, with sexual function scores reported as lower than[100] or the same as[101] controls. Adult women with myelomeningocele report poor sexual function,[102] with up to 89% having sexual dysfunction.[83,103] Many individuals find that bladder and bowel incontinence are an obstacle to better sexual function.[103]

Fertility can be impaired in women with congenital urologic disorders. This may be due to gonadal failure or anatomical obstruction, either primarily or as a result of surgical scarring. In women with differences of sex development, the majority of patients have gonads concordant with sex of rearing. However, gonads discordant with sex of rearing or gender dysphoria in adult life would impact reproductive potential.[104] In young women with cloacal anomaly, ovarian function is intact, but müllerian abnormalities often impair pregnancy ability.[88] Fertility of these individuals is unclear, although several successful pregnancies are reported in the literature.[40]

Ideally, preconception counselling would help young women with complex congenital urologic disorders make informed decisions about their own reproductive health. Review of prior operative procedures, reproductive anatomy, and concurrent medical issues such as risk for development of renal insufficiency may influence plans for pregnancy. Individuals with myelomeningocele require disease-specific counselling, such as folic acid supplementation prior to conception (to significantly reduce their risk of having a child affected by a neural tube defect) and avoidance of latex condoms.[105]

Pregnancies are at high risk for urologic complications in women who have undergone genitourinary reconstruction for myelomeningocele, exstrophy, or cloacal malformations.[88] Early pregnancy loss can be caused by müllerian abnormalities with cloacal malformations and uterine prolapse with exstrophy.[106,107] There needs to be certainty about the diagnosis of pregnancy; if there is bowel in the urinary tract, there is a false positive rate of 57% with a urinary pregnancy test. Therefore, if pregnancy is suspected, it needs to be confirmed with a serum human chorionic gonadotropin test.

Anatomical changes occurring in the gravid pelvis can increase risk of UTIs or cause urinary retention or difficulty with catheterization. Appropriate delivery planning depends on maternal bony anatomy, lower extremity flexibility, abdominopelvic muscle ability to push, assessment of urinary and fecal continence mechanisms, and anatomy/blood supply of urinary reservoirs and conduits. An elective cesarean section with shared interdisciplinary care between obstetrics and urology is often required.[88,107,108]

Congenital lifelong urologic conditions are difficult, as they encompasses a wide range of disease processes, with varied urologic concerns and potentials for problems in adulthood. Additionally, evolving psychological, social, and economic concerns influence medical treatment of these individuals. This chapter is not meant to be an exhaustive list of disorders and concerns, but to demonstrate the scope of the challenges ahead.

1.1.5.1 Recommendations for sexual/reproductive function

- Men with a history of genital surgery in childhood are at a high risk for sexual dysfunction and cosmetic dissatisfaction as they become sexually mature. Urologic follow-up through puberty and into adult life is warranted and appropriate treatment or referral to sexual health or fertility experts offered when relevant.

- Appropriate and early referral to reproductive/endocrine gynecologists should be considered for young women at risk for fertility impairment and with the congenital conditions discussed herein.

- Appropriate and early referral to maternal fetal medicine specialists should be considered for young women with the congenital conditions discussed herein.

1.2 Transition Process

Transitioning to independent, adult care for children who have grown up in a medical environment built around their congenital or childhood genitourinary condition needs to begin early and allow sufficient time for an individual to adapt. When approached as a quick switch, it leads to understandable feelings of abandonment for patients and families, subsequent fragmented care, and poor clinical outcomes. Transition should begin early, with the introduction of the idea of lifelong care to the parents of an infant or older child presenting with a genitourinary condition. Rather than avoiding conversations about the "elephant in the room" as the child grows, the plan to transition to adult care needs to be integrated into the ongoing discussions with the parents, the child, and, subsequently, the adolescent. This allows for a comprehensive transition plan to be developed with input from all stakeholders.

Overall, three broad possible courses exist for transitioning adolescents with complex genitourinary conditions. These include transferring care to a urologist with training and interest in transition (transition to new provider), continuing care with their pediatric urologist (transition with same provider), or relying on sporadic, emergency-based care without establishing care with a urologist (no transition, loss to follow-up). Transition to a new provider are the ideal course. When the necessary staff and infrastructure is available, the adult concerns of these patients can be addressed by professionals with the training and expertise to do so.

1.2.1 Goals of transition

The overarching goal of transition is to maximize quality of life and independence by ensuring uninterrupted and developmentally appropriate care as the patient transitions into adult life. These goals are aligned with the "Triple Aim" of transition: improving the individual experience of health care, improving the health of populations, and reducing the per-capita costs of care.[109] Long-term transition goals are often individualized, as they relate to physical, relational, psychological, spiritual, educational, and professional fulfilment. Therefore, it is not surprising that many of these goals may have little to do with urology. For that reason, a comprehensive transition process involves a multidisciplinary approach. At the same time, issues of continence, renal function, sexual function, fertility, and childbearing are closely linked to urologic congenital conditions, and require the continued involvement of a urologist.

Education of the adolescent in real-life care (eg, when and how to catheterize, when and how to see a physician) must also involve establishing the "why" of transition. This primarily involves establishing the reasons for regular care: to promote health and to identify and address potential problems early and to avoid deterioration. Establishing routine care is linked to fewer episodic emergency interventions, as demonstrated by one study of urology patients, in which adults lost to follow-up were more likely to visit an emergency room than those who transtioned.[110] It is worrisome that, in another study, one-third of adults who delayed transitioning did so because they were "feeling fine."[111] Although 67% of the adults who did not transition reported having new medical issues since their last urology

appointment, only 28% sought care. They most commonly obtained care from emergency or primary care physicians, both of whom are often ill-equipped to deal with the complexity of most adults with congenital urologic abnormalities.

1.2.2 Barriers to transition

Multiple barriers to transition have been identified in the population of transitioning adolescents with complex genitourinary conditions. It is not surprising that these vary with geographic location and healthcare setting. The barriers discussed below are not an exhaustive list and should only be considered as a sampling. Since studies on barriers to transition in urology have tended to be small, the relative prevalence is unclear within individual regions or countries. In addition, several barriers may apply to different individuals at different points in time. In one study, 44% of adults identified multiple barriers that delayed their transition.[111] Further work in this area is required, as 26% of participants in the same study did not identify a particular barrier to establishing follow-up, and yet had not established follow-up.

1.2.2.1 Patient- and family-level barriers

Patient and family factors include personal preferences about care (ie, forgoing routine care if not having symptoms, healthcare fatigue), education (ie, appreciating the need for and benefits of routine adult care), and self-management and support (ie, motivation for increased independence, sense of loss or abandonment, not knowing how to navigate the healthcare system, moving to another health-care environment, competing life issues). These factors may be some of the most common barriers faced by adults who do not trainsiton.[111]

An individual patient's willingness to engage in transition from parent- and physician-driven care is a key ingredient to making the process successful. A reluctance to transition has been linked to a close relationship with the pediatric urologist[112] and difficulties parents have with relinquishing parental authority.[113] In a survey of 33 teenagers with spina bifida, 40% did not want to transition (22% of parents did not either) and only 40% had considered it (89% of parents).[114] In another study, half of patients who declined to transition preferred to continue exclusively with the pediatric provider.[115] By its very definition, the transition process involves parents relinquishing healthcare decision-making to their affected child, which can be particularly challenging for parents of children with complex medical and surgical histories.[8]

A transition process that is not patient- and family-centred can also impede transition. In one study, not visiting the adult clinic before transition was noted as a barrier by patients and parents.[116] In another study, 21% of transitioning adults believed an adult hospital that was available for transitional care was inappropriate for their needs.[117] The particulars of the transition process need to be discussed in detail with the patient and family prior to the transition occurring.

As clinicians, we might expect patients who have undergone complex genitourinary reconstruction and subsequently received close follow-up to have a greater understanding of the seriousness of their condition, and thus be more likely to successfully transition than those without similar surgical

history. This does not appear to be the case; one study reported similar rates of failure to transition for these two groups.[110] This suggests that major barriers to transition appear to be independent of medical complexity.

1.2.2.2 Provider-level barriers

One of the most noteworthy barriers to transition is the lack of appropriate transition clinics for adults with congenital and childhood genitourinary conditions, particularly for those with cognitive deficits or other multisystem disabilities.[118] Many pediatric providers continue to follow adult patients due to the lack of appropriate adult specialists to transition their patients to. This has been cited as an important barrier to transition by North American pediatric urologists.[113,119] In another survey of pediatric urologists, although 64% felt that transition patients are best cared for by specialized adult providers, 54% of the transition clinics were staffed primarily by pediatric providers.[120] Therefore, the reluctance of pediatric urologists to transition is, at least some of the time, related to lack of a suitable adult care provider to whom referrals can be made. The greatest barrier to transition identified by caregivers was insufficient clinic staffing for care coordination during transition.[121] It should also be noted that delaying transfer of care may also delay the adult's readiness and incentive to transfer.[113]

Other potential, although poorly defined, limitations on the provider side to transition include lack of formalized training opportunities in adult congenital care and lack of financial resources and incentives for providers to care for this high-risk and sometimes suboptimally compliant patient population. Creative institution-specific solutions, such as those involving physician extenders and shared clinic coordinators, may help overcome the financial disincentives inherent to health care. Without appropriate care coordination, complex multidisciplinary care delivered by different providers becomes fragmented, inefficient, and ineffective.[121]

1.2.2.3 System-level barriers

Factors related to the healthcare system include health insurance (ie, lack of insurance, insurance not being accepted by a specific physician, certain services or equipment not being covered) and fragmented care (ie, challenge of navigating a new adult system, no multidisciplinary approach similar to the pediatric clinic).[111] In a fee-per-service environment, insufficient or absent health insurance coverage can be a major factor in failure to transition for adult patients with spina bifida.[113,116,121,122] In one study, it was the most common reason for not presenting for the first or subsequent transition clinic appointment.[123] Transitioning adults, especially those with cognitive or executive deficits, often find the healthcare administrative bureaucracy difficult to navigate without assistance from social workers or engaged adult healthcare surrogates (parents, adult siblings).[115]

Despite appearing to offer the best specialist care, geographic centralization of transition services to larger facilities that are often in urban centres may also impair transition, as patients often have to navigate large medical complexes, travel from long distances, and use local providers for urgent needs without involving specialty providers.[121] While increased sharing of patient information through electronic records can help bridge the gap between primary and tertiary providers, there still remain substantial impediments to care coordination for patients utilizing multiple providers.

The complexities of issues experienced by transitioning adults should not be underestimated, as they often extend beyond non-urologic medical concerns, such as chronic pain, anxiety, and depression. Failing to address a patient's financial or employment concerns was seen as a barrier to transition by patients[116] and parents.[115,116] This complexity underlines the need for a multidisciplinary approach to a safe and effective transition.

1.2.3 Transition policies

Formulating a clear transition policy is the first of six core elements of healthcare transition, which also include transition readiness, transition planning, transfer of care, transfer completion, and transition tracking and monitoring.[124] Three elements of safe and effective transition have been postulated by Viner and encompass adolescents, providers, and the healthcare system.[125] First, patients must be actively involved in the process, becoming effective partners in their own transition. Second, the clinic must be responsive to the needs of the adolescents, which often requires a cultural shift in attitudes and training. Finally, systems must be developed to ensure that all aspects of chronic illness and disability are part of the transition process, particularly in diseases where multiple organ systems are affected.

Children become adults, and thus transition is inevitable and approaching ever closer with every pediatric urology appointment. It therefore requires continued preparation on the part of the patient, family, and pediatric urologist. Explicit goals in areas of independence and self-care should be part of the routine discussion with the patient and family. Clear goals should be set with the patient's and family's involvement. Transition expectations should be explicit and parents and, subsequently, the patient him- or herself, be given the bulk of the responsibility to maintain a successful transition. The patient and their support system are the adult's best advocates.

Transition preparation should also include education and resources about the transition process (ie, how to make an appointment) and likely contingencies if problems arise, as they often do (ie, moving to new state, losing an adult provider). Written material is deemed helpful by the majority of transitioning adults.[117] Nurse educators and sometimes the care coordinator can play an important patient and family education role.

While urology providers tend to have expertise in assisting patients with knowledge and skill acquisition (ie, bladder irrigations, catheterizations), changing patients' attitudes and teaching real-world decision-making (ie, interest in self-care, troubleshooting in social situations) are often outside of the scope of normal practice. New ways of educating and engaging patients need to be developed for these critical skills to be internalized.

1.2.4 Transition planning

Readiness for transition to adult care has been studied in multiple chronic conditions. Transition readiness encompasses five components: time devoted to the process, knowing and understanding the process, level of interest in learning more about transitioning, areas of concern, and acknowledgement of the importance of lifelong follow-up with an adult-urology specialist.[126] Given the complexity of transition, the process needs to be an explicit and mandatory long-term project. Anticipatory

planning is paramount and should include formally presenting the adolescent and family with the transition policy when the patient is about 12 years old. This is followed by a formal assessment of the long-term needs by the pediatric team, and subsequent preparation for transfer.[118,127] A well-planned transition process is iterative, addressing the concerns of all those involved in the process. A feedback mechanism is needed to allow for adaptability and individualization, but few clinics have one in place.[121]

While the transition point of about 18 to 20 years old has been suggested,[117] adopting a strict age cutoff can be problematic and often not feasible. Rather, the process should be flexible, coordinated, and individualized, given different levels of psychosocial development, medical needs, and readiness to transition.[115,116] Additionally, this may be influenced by regional or national government policies. Despite these challenges, a clear plan and guidelines should exist for this process. Without them, patients' and families' confidence and interest are eroded, and a safe and effective transition is less likely to occur.

Transition to an adult provider can occur rapidly, with a final pediatric visit followed by the first adult visit, or more gradually, with both pediatric and adult providers overlapping for one or more visits. While overlapping visits facilitate the building of communication, patient confidence, and the adult medical record, this approach is feasible only in select settings.[116,118] In either approach, an accurate and thorough medical summary is integral for transfer of care.

In addition, no single transition plan will be adequate or appropriate for all geographic locations and healthcare systems. It will be influenced by local resources and adapted to the needs of a growing child and guided by their support system. It must be adjusted to the particular limitations pertaining to provider- and system-level barriers, including available specialists, ancillary staff, financial resources, institutional interest, and physical space.

1.2.5 Tracking and monitoring

If the goal is to ensure that ever-more adults with congenital urologic conditions transition successfully, both success and failure must be precisely defined. Without these definitions, the outcome is vague and improvement impossible. These definitions can and should develop over time, but any reports on transition must contain workable definitions. Setting even an arbitrary cutoff will allow for an assessment of the status quo, a meaningful comparison between centres or models, and identification of patients at risk of an unsuccessful transition. Patients and families need to be an integral part of this discussion, as they are the ones in the trenches of transition and have intimate knowledge about the process that is not available to subspecialists. Finally, clearly formulated definitions developed by different groups can be critically compared and used to guide the discussion around transition using actual data, as most discussion of this process is theoretical and anecdotal.

Two studies have defined successful transition as attending a single transitional urology appointment within a set time period after the last pediatric urology appointment; one study defined the period as 18 months, and the other as 24 months.[110,111] These simplistic definitions equate making contact with a transitional urologist with a successful transition but provide an initial workable definition. In a more comprehensive sense, a successful transition needs to be timely (occurs within a set length of

time after discharge from a pediatric provider), lasting (consist of several appointments during a set length of time), and associated with increased independent self-care (limited reliance on caregivers). This more complete definition suggests that, upon first attending a transition clinic appointment, different levels of success are possible. Limited literature exists on how transitioning adults stratify when it comes to level of successful independence.

It must be noted that, despite a well-planned transition process, some patients will still be lost to follow-up.[110,118] As few as half may transition or remain in the care of their pediatric provider, despite implementing multiple transition options.[110,115] Predictors of successful transition in urology and ways to improve it remain largely unknown and deserve detailed study.

Age at transition varies widely within and between centres. Depending on the study, average age at establishing transition clinic follow-up ranges between the early 20s to the late 30s.[43,111,115,116,123] Since it is unclear when many of these patients actually left pediatric practice, the length of the care gap remains unknown. Comparing effectiveness of transition between centres should involve an assessment of how well the transition process has been adapted to different settings and patient populations, acknowledging that some of the constraints are not easily surmountable.

Finally, whenever possible, data should be collected using validated tools, especially ones designed for and with people with congenital urologic conditions. These specific tools do not yet exist. A popular validated generic tool is the Transition Readiness Assessment Questionnaire (TRAQ), which assesses transition-related behaviours.[128] Although widely used, TRAQ is a generic instrument and does not address urology-specific needs or behaviours. It is therefore a limited tool and an inadequate guide to formulating actionable targets for transition planning.

1.3 The Transition Team

1.3.1 Creating a transition team is an important element of successful transition

When considering the basis of a transition team, a number of core principles should be considered. A transition team may consist of as few or as many members as is deemed necessary based on local service arrangements. A minimum requirement should be determined, and this should be applied consistently to all young people requiring transition. An example of a core transition team might include:

- Lead clinician
- Named specialist nurse or physician extender
- Transition coordinator
- Clerical secretary or administrative assistant to handle administrative tasks
- Community services coordinator or social worker

1.3.1.1 Lead clinician

The lead clinician will have full knowledge and understanding of the background diagnosis, treatment received to date, ongoing problems and challenges, and future care needs. Ideally, but rarely, this individual has been present in the patient's health care throughout at least some of childhood, and so there is an established therapeutic relationship between provider, family, and other key healthcare inputs for the child's life. A discussion between the lead clinician and the young person with their family/advocate will reach a stage whereby the process of preparation for transition will begin with an agreed future target date for transfer of care.

The lead clinician may be a pediatric urologist if the primary disability experienced by the patient is urologic in nature (eg, exstrophy) but, for multisystem diseases, it is best to have a primary care provider in this role.

The availability of adult urologists with a special interest in caring for such patents varies greatly across healthcare systems, and the specific arrangements in place in any local, regional, or national setting will depend heavily upon expertise and appropriate service design. Any urologist receiving young adult patients with transitional care needs due to congenital lifelong urologic conditions must have a good understanding of the relevant pathophysiology of the urinary tract, congenital anatomy, and surgical anatomy; be able to be responsive to patient-specific care needs; and have the correct skills and equipment available to troubleshoot emerging problems in a timely manner. For example, a young person struggling to catheterize a Mitrofanoff channel with pain in his augmented bladder and blood in his urine should expect to receive attention without delay from a urologist fully capable of endoscopic evaluation using appropriate instruments and able to manage unexpected findings such as a bladder calculus.

1.3.1.2 Specialist nurse, nurse practitioner, or other specialist physician extender

In many clinical circumstances, the appropriate person to act as a first point of contact is a specialist nurse or physician's assistant/extender. As mentioned above, healthcare systems' abilities to support a provider may be limited by compensation provisions and resources made or not made available through governmental support.

However the role is defined, the individual should have comprehensive knowledge of the full range of congenital urologic conditions and should be familiar with the details of each individual young person entering the period of transition to adult care.

This individual should be present at transition clinic appointments and be integral in care planning for each young person, and serve as the first-line provider in urgent or chronic ongoing health care needs as they arise (refills on prescriptions, orders for urine cultures, etc).

1.3.1.3 Transition coordinator

In some larger pediatric hospitals, where transitional care occurs across multiple specialties, a transition coordinator plays a vitally important role in keeping transition planning moving ahead at an appropriate pace. This will include ensuring that appointments are made at convenient times for the young person and their family in order to minimize wasted hospital resources through missed appointments and to maximize the effectiveness of the transition or transfer process. Maintenance and documentation of transition milestones is often the responsibility of the transition coordinator and clerical secretary.

Dedicated time and funding for this work is essential, but can be difficult to obtain. Reported benefits of care coordination include improved follow-up, fewer hospitalizations, improved communication between providers and patients, patient empowerment, more efficient connections with community resources and supports, and reduced caregiver strain.

In an interesting analysis of their experience with the dissolution of a multidisciplinary spina bifida clinic, Kaufman and colleagues point to lack of a clinic coordinator as a critical point of failure: "It is unrealistic to expect the continuation of effective care by merely maintaining the individual services of the disbanded clinic, without some coordinator of care." They go on to detail the significant deterioration in care for their patients. Decentralized, uncoordinated care has been recognized as problematic in the primary care world, which has responded with the creation of the patient-centred "medical home." Multidisciplinary clinics can be considered a tertiary medical home for complex patients. The Patient Protection and Affordable Care Act (2010) passed in the United States advocates both the medical home model and the provision of care coordination and case management services as important strategies to ensure quality health care and improve health outcomes.

1.3.1.4 Clerical secretary/administrative assistant

An efficiently managed transition or transfer system is greatly enhanced by the involvement of a clerical secretary or administrative assistant who works closely with the lead clinician, specialist nurse, and transition coordinator. A clear understanding of the care pathway being used and the ability to monitor the progress of each young person during their individual transition journey is pivotal to success, and the integration of a secretary or administrative assistant into the transition team to maintain clear and accurate administrative tasks is a vital element.

1.3.1.5 Community services coordinator/social worker

Community services while under pediatric care may not be mirrored after transition to adult health care. A coordinator of services based in the community can offer enormous support and may serve to help the patient and family navigate the often disjointed community and health services organizations and agencies that they often face after the patient completes his or her primary education. Such community-accessible services may include obtaining physiotherapy and occupational therapy; psychology services; prescription items such as catheters; transportation services; employment and vocational skills services; financial aid and secondary education support; and housing support.

1.4 Transitional Care: Multidisciplinary Teams

As mentioned above, the core transition team typically involves a single physician provider serving in the role as lead clinician. However, for conditions involving multisystem diseases (eg, spina bifida) and of sufficient complexity that multiple pediatric specialists have been involved in patient care, coordination and contribution by all members of the care team is necessary to ensure uninterrupted care into adult life.

As with any clinic, a multidisciplinary service requires engaged providers with appropriate expertise. Many transition clinic models describe the benefits—for both patient and provider comfort—of joint visits with pediatric and adult providers. If possible, the pediatric providers should avail themselves to the adult providers indefinitely. At the very least, pediatric providers must provide a comprehensive medical summary to their adult counterparts.[119] While pediatric multispecialty clinics often have a generalist such as a developmental pediatrician or physiatrist overseeing patients' care, such providers in adult multidisciplinary clinics are scarce.[129] Clear communication between multidisciplinary specialists and adult primary care providers is thus all the more important, and can be facilitated by the clinic coordinator.

Other members of the medical multidisciplinary team may include dietitians, wound and stoma nurses, mental health providers, physical and occupational therapists, nurse educators, and more. Nonmedical team personnel are equally important and include social workers, financial counsellors, and research coordinators.

1.4.1 Urologic conditions requiring multidisciplinary care

1.4.1.1 Spina bifida

The need for multidisciplinary care in transition is, perhaps, best demonstrated in spina bifida, and multidisciplinary spina bifida transitional clinics serve as the prototype for transitional care in urology. This is a common condition with significant, varied, and ongoing medical and nonmedical needs. Improvements in early medical and surgical management of neurogenic bladder, hydrocephalus, neurosurgical closure, and infection have successfully decreased pediatric mortality; subsequently, 75% to 90% of patients are now living into adulthood.[116,130-132] Despite advances in recent decades, medical morbidity and early mortality are higher when compared to healthy cohorts. In a robust community-based study of long-term outcomes in spina bifida patients in England, Oakeshott and colleagues found mortality rates in older children and young adults with spina bifida to be 10 times the national average.[133] Half of deaths were sudden and unexpected. Cause of death spanned medical specialties and included epilepsy, pulmonary complications, acute hydrocephalus, renal failure, and sepsis due to UTI. Survival correlated strongly with the level of the neurologic deficit, though even patients with the mildest deficits (sensory levels below L3) exhibited a meager 61% survival rate past age 40 years. Renal failure is no longer the leading cause of death. In two studies with follow-up periods of more than 10 years, mortality related to renal failure is reported as 0% to 0.5%.[134,135]

1.4.1.1.1 Urologist

The urologist's role in both pediatric and adult life for patients with spina bifida is discussed in great detail in **Chapters 2 and 3** of this consultation. Urology specialty care begins at birth with a focus on aggressive bladder management in the interest of renal preservation, infection prevention, and, later, continence with the pediatric urologist. This continues into adolescence and adult life with management of concerns around sexual function, fertility, and age-related acquired urologic diseases (eg, pelvic organ prolapse). Prevention and management of complications from treatments for any of these, as with augmentation cystoplasty, presents yet another critical, life-long role for the urologist. Failed ongoing care and poor surveillance of patients can often lead to sometimes irreversible and morbid outcomes for patients with spina bifida.

1.4.1.1.2 Neurosurgeon, neurologist

In addition to the primary neural tube defect, many spina bifida patients have congenital or acquired hydrocephalus. Issues related to hydrocephalus require shunting in approximately 80% of people with spina bifida.[136] Ventriculoperitoneal shunting in childhood has generally been credited with improved early outcomes.[137] We are starting to understand long-term functional outcomes in successfully shunted patients. In one large, longitudinal series, only 18% of shunted patients were free from neurologic sequelae of hydrocephalus.[138] The remainder suffered from motor, cognitive, or behavioural deficits; epilepsy; vision loss; endocrine disorders; and more. Unfortunately, the long-term durability of ventriculoperitoneal shunting is low, and few patients become truly shunt-independent in adulthood.[138,139]

Moreover, recognition of shunt failure in the adult population is not always straightforward. Whereas acute-onset hydrocephalus in adults nearly always presents with dilation of the ventricles, nearly 25% of patients with congenital hydrocephalus and shunt failure will have "normal-volume hydrocephalus," or noncompliant ventricles that do not dilate in response to elevated intracranial pressure.[138] In addition to shunt malfunctions, patients with spina bifida have type II Chiari malformations and syringomyelia, which have unique clinical manifestations in the myelomeningocele population and require long-term monitoring.[140] Spinal re-tethering, while classically described during adolescence, can occur at any point along the lifespan and may manifest or exacerbate common acquired spinal diseases such as disk herniation or spinal stenosis in later adulthood. A neurosurgeon familiar with these problems is paramount throughout the lifespan, not just in pediatric life.

1.4.1.1.3 Orthopedist, physiatrist, physical therapist

Musculoskeletal problems plague many patients with spina bifida and may progress over time. Common conditions include scoliosis, kyphosis, joint contractures, foot deformities, hip subluxation, and gait abnormalities in ambulatory patients.

Growing and adult spina bifida patients can suffer progressive musculoskeletal pathology necessitating ongoing orthopedic care. Secondary cord tethering and syringomyelia are neurologic problems seen in growing or adult spina bifida patients who frequently present with orthopedic sequelae. Progression of kyphoscoliosis can lead to restrictive lung disease, a source of significant morbidity in the adult spina bifida population. Immobility and obesity can exacerbate these conditions over time

and contribute to premature skeletal aging. Ongoing physical therapy is necessary to maintain supple joints and range of motion, and lack thereof is known to lead to functional decline and even loss of ambulation.[141,142]

1.4.1.1.4 Gastrointestinal health

Neurogenic bowel is very common among spina bifida patients. Eighty percent of patients with spina bifida will need to be on some sort of bowel program.[141] Fecal continence is known to correlate to quality of life, and may be one of the most important social determinants of success.[143] Analysis of the National Spina Bifida Patient Registry, in the United States, reveals complete fecal continence rates of 58% in the adult spina bifida population. Continence was significantly associated with employment status, private insurance, and education level.[144] Importantly, bowel dysfunction may progress throughout a patient's life, and management strategies that work well in pediatric life may fail in adult life, necessitating gastrointestinal evaluation and sometimes intervention. In addition, bowel management routines that rely on lifting and transferring the patient and assistance by another care provider (eg, enemas) may become extremely cumbersome as the patient ages. A gastroenterologist or general surgeon comfortable with bowel management is a requisite part of the multidisciplinary care team. When conservative measures fail, a surgeon may need to be involved for creation of an antegrade colonic enema channel, troubleshooting stomal stenosis or prolapse, or colostomy creation.

1.4.1.1.5 Sexual health, fertility, and pregnancy

With spina bifida patients living into adolescence and adulthood, matters surrounding sexual health, fertility, and pregnancy become more relevant. Genetic counselling prior to consideration of parenthood is recommended for both men and women with spina bifida. In-depth discussion of male sexual needs and male and female fertility needs can be found in **Chapters 3 and 6** of this consultation.

Men and women with spina bifida have divergent needs in this domain. Subspecialty gynecologic care, including reproductive/endocrine/infertility, maternal fetal medicine, and reconstructive gynecology, may be necessary at different points along the lifespan. The urologist will often interface with all and serve as co-provider at critical junctures.

For example, as the gravid uterus enlarges, bowel and bladder care can be affected, and up to 60% of patients will require an indwelling catheter for bladder drainage.[141,145,146] There have been multiple reports of ventriculoperitoneal shunt obstruction secondary to compression, kinking, or increased intra-abdominal pressure during pregnancy.[147] Hydronephrosis requiring percutaneous drainage and pyelonephritis are common.[145,146] Labour presents its own challenges. Patients with impaired sensation may not recognize uterine contractions or may interpret loss of amniotic fluid as urinary incontinence.[141,147] An obstetrician with specialty experience in high-risk pregnancy should play a central role in determining prior to labour which delivery plan is safest for mother and child. Issues pertaining to lower extremity contractures, previous abdominal and pelvic surgery, fetal position and health, and maternal health all play into this, as do geographic challenges and provider availability. In those patients who have undergone urinary tract reconstruction, if the obstetrician feels cesarean delivery is prudent, a urologist should be available to assist in the surgery to provide surgical exposure for the delivery team.

Gynecology may only be sporadically involved with female patients having spina bifida (eg, depending on sexual activity) and urologists tend to see patients at regular intervals, so the urologist may play an important role in re-referrals to a gynecologist when appropriate.

1.4.1.1.6 Social work

A major part of successful transition is imparting the tools needed for patients to care for themselves. Navigating the healthcare system can be daunting for any patients. But for those with complex care needs, the challenges can seem insurmountable. Patients commonly report difficulties with insurance, transport, finances and employment opportunities, and not being aware of the available resources and/or how to access them.[121,123] A social worker or care coordinator can be the critical intermediary here, bolstering both patient care and patient self-advocacy.

1.4.1.1.7 Nutrition

Obesity is nearly universal in the nonambulatory adult spina bifida population and complicates nearly all aspects of care, including catheterization, hygiene and skin care, pulmonary function, and any necessary surgical intervention. It also increases the risk of diabetes and metabolic syndrome, with the associated cardiovascular sequelae. Malnutrition related to prior utilization of bowel segments and subsequent malabsorption and poverty often co-exists with obesity in this population.

1.4.1.1.8 Wound care

Skin breakdown is a common concern across the lifespan, but increases in prevalence and morbidity as patients progress into adult life. Immobility, obesity, insensate skin, wheelchair use, lymphedema, and skin moisture from urine leakage are among the contributing factors. Patients and families should be educated on skin health, as it is much easier to prevent skin breakdown than to treat it. Recent studies show that 20% to 30% of adult spina bifida patients have developed decubitus ulcers.[148,149] These wounds can be a source of significant morbidity, lead to osteomyelitis, and, in severe cases, may require urinary and/or fecal diversion and flap closure.

1.4.1.1.9 Mental health

As children become older and develop self-awareness, the psychosocial challenges of adolescence and adulthood come to the forefront. Normal teenage rebellion can manifest as apathy toward self-care and, unfortunately, can have long-lasting effects. Poor compliance with self-catheterization regimens is common. Substance abuse may become an issue, and some substances have temporary or permanent physiologic effects, particularly on bladder, renal, or sexual function.[118] While many children with spina bifida have good verbal skills, there is some evidence of occult learning disabilities and/or cognitive dysfunction in some patients, perhaps related to hydrocephalus.[150,151] Disability itself places patients at risk for depression, and unfortunately women with disability are vulnerable to sexual exploitation.[141,152] The availability of a mental health provider attuned to the special needs of patients with disabilities is an important component of whole patient care, although there is undeniably a knowledge void in this field.[118]

1.4.1.2 Bladder exstrophy, epispadias, cloacal exstrophy

These children require continuous urologic care from infancy. Patients with cloacal exstrophy will have additional morbidities related to their bowel and neurologic system; classical bladder exstrophy and epispadias tend to occur in isolation. Although there will be the rare patient with isolated

epispadias who has normal urinary function and sexual function with minimal surgical intervention, nearly all patients with these disorders will need transitional care. In-depth discussion about the urologist's role in pediatric and adult bladder management and sexuality and fertility management are contained in **Chapters 2 to 6** of this consultation. The needs for additional medical specialists in adulthood will relate to the degree of urinary, sexual, reproductive, and bowel dysfunction present. Additionally, there are possible needs due to orthopedic and neurosurgical comorbidities. Finally, it cannot be overemphasized that an underappreciated mental toll these deformities take on our patients frequently results in psychological problems that extend into adulthood.

1.4.1.2.1 Orthopedics and neurosurgery

All exstrophy patients have some degree of pelvic diastasis, resulting in abnormalities of the pelvic ring and floor. There is external rotation of the posterior pelvic bones, retroversion of the acetabulum, and external rotation and shortening of the pubis with a wide diastasis.[153] Coincident with these changes in the bone are abnormalities in the muscles of the pelvic floor. Computed tomography studies have shown that there is a greater bulk of levator muscle located posterior to the anus and less anterior to the anus and posterior to the bladder.[154] The result of these complex deformities of the pelvis is increased risk for pelvic floor prolapse in females. Additionally, long-term studies have suggested that there is a higher incidence of hip and lower back pain in these patients.[155,156] There are some data suggesting bowel incontinence is more likely than expected in exstrophy patients, which may be due to these changes in the structure of the pelvis.[157]

Adult patient surveys have reported higher rates of pain in patients who underwent pelvic osteotomies during initial closure. Numbers were low, making conclusions difficult, but raise the possibility of the need for future orthopedic care as an adult.[155]

Patients affected with cloacal exstrophy are much more likely to need orthopedic and future neurosurgical care.[158] Ninety percent or more will have a spinal anomaly such as a tethered spinal cord. Scoliosis is a progressive problem in a minority and patients may also have lower extremity anomalies due to neurologic deficits. About 85% of patients with cloacal exstrophy can walk, but about 15% of those need to use supportive devices. Those with hydrocephalus and ventriculoperitoneal shunts will need long-term neurosurgical care, but all carers need to be aware of the risk of neurologic sequelae and the potential need for referral.

1.4.1.2.2 Female pelvic reconstructive surgery and obstetrics

The pelvic deformity that accompanies bladder exstrophy has implications that can lead to pelvic floor problems during adulthood.[154] The combination of a stenotic, shortened vagina and prior reconstructive surgery make pregnancy high risk.[107,156,159] Successful pregnancies in women with bladder exstrophy are well documented.[107,146,156,159,160] Screening and early referral to gynecologists specializing in reproduction/endocrine/infertility and/or maternal fetal medicine should be offered to all young women interested in becoming pregnant. Additionally, genetic counselling may also be considered, as historic data have suggested an increased risk to offspring;[161] however, long-term experience and data have not led to a confirmed genetic link.

Cesarean section is often advised due to the pelvic and vaginal concerns. Up to half of adult women with bladder exstrophy develop prolapse.[95] Postpartum, it is estimated that up to 50% of women will develop prolapse. Depending on the degree of prolapse, treatment is not always needed. When prolapse progresses or is severe, treatment should be planned considering the patient's surgical history, desire for intercourse, desire for future fertility, and comorbidities.[162] The prolapse should be addressed by a surgeon with considerable experience in pelvic reconstruction and preferably some experience with bladder exstrophy. Outcomes are reported to be best with transabdominal rather than transvaginal approaches, which often include sacrocolpopexy in some form.[156,162]

1.4.1.2.3 Gastroenterology

Fecal incontinence is a common problem for patients with cloacal exstrophy. The prevalence is difficult to assess, as many will have either a permanent ostomy or are in need of a chronic bowel program if they underwent a coloanal pull-through. This will often include enemas and may include a cecostomy. At the age of transition, these patients should be referred to a colorectal or general surgeon with an interest in continuing the bowel management of these patients. Parastomal hernias and issues with appliance fit often occur later in adulthood, and the expertise of a good wound-ostomy care nurse may be needed to make appliance recommendations. Alternatively, the patient could be followed in a multidisciplinary clinic that manages patients with spina bifida, since, for the most severe cloacal exstrophy patients, spina bifida is present. Patients with classic bladder exstrophy have not been thought of as at risk for fecal incontinence and bowel dysfunction. However, based on the anatomical deformity that occurs in the levator muscles of the pelvis, it is not surprising that about 20% of adults with bladder exstrophy report some day or night fecal incontinence.[157] This is worse in patients who have undergone a ureterosigmoidostomy or bladder reconstruction that used bowel. In addition, those patients who have a urinary diversion with a ureterosigmoidostomy have a need for gastrointestinal cancer surveillance and will need to be referred to a gastroenterologist. Again, it is important to educate adult specialty providers about the unique needs and risks of this patient population, due to its rarity.

1.4.1.2.4 Mental health

While typically considered to have normal intelligence and be normally functioning, there is a high rate of clinically significant anxiety disorders in exstrophy patients. The anxieties are related to concerns about urinary continence, sexual function, body image, and medical interventions.[163] Internalizing symptoms are more common in children with exstrophy (anxiety, depression, somatization). Males have been shown to have poor adaptive functioning that is more prominent as they age. Males more commonly show externalizing behaviours (hyperactivity, aggression, conduct problems) as they get older.[164] Importantly, there is a higher risk for depression and suicidal behaviours in these patients, as well.[165] Given what has been learned about the psychological state of these patients, it is recommended that they be under the care of a pediatric psychologist during childhood and should be transitioned to an adult mental health provider.[164] Given the rarity of this disease, the provider should be carefully chosen. Again, it is important for the urologist to make contact and educate the provider regarding the aspects of bladder exstrophy that are affecting the patient.[165]

1.4.1.3 Anorectal malformations (ARMs), cloacal anomalies, and other neurogenic bladder

Anorectal anomalies occur over a wide spectrum. Cloacal anomalies in females are the most severe form. There are high rates of congenital abnormalities of the urinary tract in these patients. Patients with more severe forms often have spinal anomalies (vertebral anomalies, scoliosis, tethered spinal cord, sacral agenesis) and are at high risk for neurogenic bladder dysfunction.[166] It is the need for continued bladder management that will keep these patients under the care of the pediatric urologist. While some would consider this disorder one that would typically transition under the care of pediatric surgery, bladder dysfunction and kidney monitoring will require the need for continued urologic input. Additionally, early reviews of the transition process shows that patients struggle with not being prepared and with difficulty finding adult providers with knowledge or experience of their disorder.[167]

1.4.1.3.1 General or colorectal surgeon

Studies looking at the status of long-term patients with ARM suggest that bowel incontinence and the need for continued bowel management remain an issues for up to 76% of patients.[168] Ensuring that patients continue care under a knowledgeable colorectal or general surgeon will help them to have continued success with bowel programs and hopefully minimize the numbers that ultimately get treatment with a permanent stoma. As mentioned above, the continued services of a stoma nurse specialist are important for patients with colostomies and ileostomies throughout the lifespan.

1.4.1.3.2 Gynecology and obstetrics

Females with ARM have a significant risk of abnormalities of their reproductive tract. These range in severity from duplication anomalies to vaginal agenesis.

It is critical for the treating pediatric surgeon to document the anatomy of the reproductive tract during the initial treatment. It is recommended that female infants with ARMs have vaginoscopy performed as infants to evaluate the status of the vagina and cervix. This will allow for the detection of vaginal agenesis, vaginal septum, and duplication anomalies, including cervical or uterine duplication. This information needs to be preserved and passed on to the patient and their adult providers, as there can be impairment of fertility and increased risks associated with some of these anomalies. Pregnancy is considered high risk with these patients. In those with urinary diversion or reconstruction, additional risks may be present, including difficulty with catheterization, recurrent UTIs, and difficulty and increased potential risks with vaginal delivery.[146] Preconception delivery planning would be ideal but, at the very least, early delivery planning, including a joint consultation between the obstetricians, the general surgeons, and the urologist that are managing the patient, is necessary. Cesarean delivery plans should bear in mind the potential effects of the patient's prior surgery. Screening and early referral to gynecologists specializing in reproduction/endocrine/infertility and/or maternal fetal medicine should be offered to all young women with ARMs.

1.4.1.4 Differences of sexual development/intersex disorders

The term disorders of sexual development was adopted in 2006 at a consensus meeting, and later re-termed differences of sexual development (DSD).[59] DSD encompasses a vast array of genital, gonadal, and chromosomal abnormalities. Historically, these conditions have been called intersex disorders; some still prefer this term. Interest in multidisciplinary transitional care is growing due

to ongoing medical and surgical needs in DSD patients, as well as unique issues that arise in adolescence and young adulthood.[169-171] Multiple specialists are necessary to achieve hormonal, sexual, reproductive, and psychological health in these patients.

1.4.1.4.1 Urologist

For infants and young children presenting with DSD who require surgery, pediatric urologists are often the primary surgeons. Potential surgical intervention involves abdominal/laparoscopic exploration for reproductive structures, attention to *in situ* gonads, and genitourinary reconstruction. In the transitional setting, the role of the urologist includes addressing long-term functional and cosmetic outcomes of genitoplasty, urinary symptoms, and—in concert with endocrinologists and gynecologists—sexual function and fertility. An in-depth discussion of the urologic aspects of care for patients impacted with DSD is contained in **Chapters 3 and 6** of this consultation.

Not all patients with DSD have undergone surgery in early childhood. A subset of those will elect to undergo surgery in adolescence or adulthood. Urologists may work in concert with gynecologists and/or reconstructive surgeons to address gender-affirming genitoplasty and/or removal of internal genitalia.

1.4.1.4.2 Gynecologist

A gynecologist may be the first point of contact for DSD patients not diagnosed in infancy. Phenotypically female patients can present later in life with amenorrhea, pubertal delay, virilization at puberty, vaginal shortening and sexual difficulties, or infertility.[172] For older DSD patients who have not had reconstructive surgery, gynecologists may direct vaginal dilation or assist with vaginoplasty, gonadectomy, or hysterectomy. For patients who have undergone feminizing genitoplasty, long-term gynecologic complications requiring revision surgery are common. Vaginal stenosis and scarring can lead to difficult or painful dilation. Revision labiaplasty or vulvoplasty can improve the cosmetic appearance of the vulva. As patients transition to adulthood, these issues traditionally fall within the gynecologist's scope of practice.

1.4.1.4.3 Endocrinologist

Ongoing follow-up with an endocrinologist is critical for nearly all DSD diagnoses. Endocrine work-up is central to establishing a diagnosis, which in turn dictates the widely varying hormone needs amongst DSD patients. The role of the endocrinologist includes, but is not limited to, sex hormone supplementation and suppression, monitoring bone health and growth, mineralocorticoid and glucocorticoid therapy and associated electrolyte and blood pressure monitoring, and optimizing fertility, when possible.[170] For patients with poorly functioning or surgically absent gonads, sex hormone replacement therapy is often necessary to induce puberty and must continue through late adulthood.[171-173] In conjunction with surgeons and patient families, the endocrinologist also gives valuable input regarding timing of gonadectomy, a decision that takes into account fertility, gonadal function, gender correspondence, and risk of malignancy.[170]

1.4.1.4.4 Fertility specialist

Fertility in DSD patients is the joint domain of the urologist, gynecologist, and endocrinologist. As in any person with a genetic anomaly, genetic counselling would be prudent prior to considering parenthood. Infertility in DSD can result from abnormal gonadal development, hormone imbalances, or

structural problems with internal or external genitalia. A recent comprehensive review of fertility in DSD patients provides insights into fertility potential–based specific diagnosis.[174] Fertility potential appears to be highest in patients with XX or XY congenital adrenal hyperplasia, particularly nonclassic forms. Fertility rates in females with CAH are inversely proportional to the severity of the disease. Fertility is rare in pure or mixed gonadal dysgenesis, ovotesticular disorder, and XX males. Assisted reproductive technologies have broadened fertility options for some DSD patients and include egg donation, surrogacy, hormonal manipulation, testicular sperm extraction, and intracytoplasmic sperm injection.[170]

1.4.1.4.5 Psychologist

The psychological sequelae of a DSD diagnosis are difficult to characterize. Available data are limited. Patients are heterogeneous, sample sizes are small, study methods are neither standardized nor systematic, and funding for research is scarce. Still, the need for psychological health care among DSD patients is well accepted. Psychological distress in the DSD population is more prevalent than among non-DSD peers and, in small studies, early mental health support appears to decrease this distress.[175] More than the typical adolescent, the DSD patient has complex body image, identity, and romantic concerns. Psychological distress arises from issues surrounding disclosure and social stigmata of their diagnosis, sexual anxiety or dysfunction, gender dysphoria, and infertility—all of which can intensify through adolescence and young adulthood. Attention to these issues throughout development would not only benefit individual patients, but also could help providers better understand these poorly understood aspects of DSD.[173]

1.4.1.5 Additional specialists for select conditions/situations

1.4.1.5.1 Nephrologist

There are a number of congenital urologic conditions that require follow-up with multiple specialists into adulthood. The nephrologist is a common partner for the urologist and is needed for follow-up of all patients with chronic kidney disease (eg, posterior urethral valves, prune belly syndrome), metabolic stone formers, and more. A more detailed discussion about the nephrologists' role in congenital urologic care is included in **Chapter 5** of this consultation.

1.4.1.5.2 Oncologist

Patients with a history of childhood abdominopelvic malignancies may also need long-term multispecialty follow-up. Most of these patients will have undergone surgery, chemotherapy, and/or radiation. Cancer survivorship clinics may address many long-term follow-up needs; however, the risk of ongoing skin, bladder, and bowel problems and future fertility and sexual dysfunction may necessitate follow-up with multiple specialists. Pelvic radiation, in particular, poses risks for stricture disease, fistula formation, bladder dysfunction, radiation cystitis, dyspareunia, erectile dysfunction, and infertility. For such patients, coordinated multidisciplinary care will be rare. Even without a formal transition program, pediatric urologists should cultivate relationships with trusted partners in the adult world with the goal of establishing long-term care for their patients before they move on from pediatrics.

1.5 Systems Required for Success

A major obstacle requiring successful systems for transitioning patients with congenital urologic conditions lies in geographic and economic differences. Globally, enormous differences exist between hospitals and compensation systems, which make a unifying framework challenging. Many urologic conditions that require careful transition to adult services are, by definition, multidisciplinary and require cooperation from other specialties, including neurosurgery, orthopedics, general surgery, gastroenterology, psychiatry, nephrology, endocrinology, and physiatry, with hospitals ideally staffed with all these departments. Coordination of these subspecialties, particularly streamlining communication from all relevant stakeholders, is inefficient and administratively costly by its very nature. The geographic distances between pediatric and adult care hospitals and clinics can be substantial to allow for effective coordination and continuity of transition, especially in geographically expansive countries with heterogeneous healthcare systems such as the United States. Other issues such as healthcare provider/patient bias and enabling the patient to actively care for their own needs are outside the scope of this, but can interplay with complex social factors beyond the obvious financial implications of transition.

1.5.1 Funding

Multidisciplinary clinics are not profitable ventures. To most hospitals, a multidisciplinary spina bifida clinic is at best revenue neutral, and typically a money loser.[176] The high burden of indirect care incurs costs that are seldom reimbursable. There are challenges billing for multiple providers' services during a single visit. Most multidisciplinary clinics depend on the support of their hospital, their parent organization, or philanthropy. Buy-in from departmental- or hospital-level leadership is necessary prior to instituting a multidisciplinary clinic.[177] There is little published about the cost savings incurred by preventive care, and such information is notoriously difficult to capture. Financial viability may require innovative partnerships between providers, philanthropic organizations, patients and patient advocates, insurance providers, and government agencies.[129]

1.5.2 Facilities

A multidisciplinary clinic requires a physical space that accommodates multiple providers, special needs patients, and equipment for therapists on site. There should be a nearby or on-site imaging facility and laboratory. Ideally, there would be reserved radiology slots for routine follow-up imaging, such as renal ultrasounds and brain magnetic resonance imaging. As telemedicine becomes more sophisticated, those developing multidisciplinary clinics may consider installing telemedicine suites to provide remote care to patients with transportation barriers.

1.5.3 Additional infrastructure

Conferences or other opportunities for sharing interdisciplinary knowledge should be built into the multidisciplinary clinic schedule. Patient-centred conferences allow for whole-team discussion of complex patients and unified care plans. Team meetings are important to evaluate clinic performance and review successes and opportunities for improvement. On clinic day, there must be a system for tracking patients through their visits with multiple providers. Between clinic days, a patient tracking system should be in place to ensure patients are not lost to follow-up. A separate data capture system for research purposes is important to further the field; for many hospital systems, the electronic medical record may suffice.[177]

1.6 Systems Recommendations

The concept of medical transition has been endorsed by a number of organizations, including the American Academy of Pediatric, the American College of Physicians, and the American Academy of Family Physicians.[124] Hsieh *et al.* describe how only 68% of spina bifida units have a written transition policy, and that testing, validation, and comparative analyses of various models of transitional care are required to organize and deliver the best care to this cohort of patients.[178] From an insurance perspective, families would be sensible to find out when their insurance policies end and what alternatives might be available, and to apply for them in a timely manner to avoid any unforeseen consequences with regards to coverage.

As mentioned above, a dedicated transition coordinator who acts as a conduit between both pediatric and adult hospitals who can then ensure timely and seamless transfer of patients between systems is a fundamental component of a successful transition system. In addition to this, other systems recommendations include:

1. Adopting a written transition policy for those requiring transition to adult services;
2. Highlighting the importance of insurance following the patient, not the institution, and therefore attempting to avoid loss of coverage between hospitals;
3. Acknowledging that electronic medical records between hospitals need to be able to cross talk in order to allow for seamless transition of letters, results, and image files;
4. Ensuring that transitional clinic and adult facilities are equipped to deal with the examination and treatment of patients with disabilities;
5. Recognizing the importance of subspecialty training and workshops for those healthcare providers involved in transitional care;
6. Developing a standardized transitional healthcare pathway to facilitate transition and data flow between healthcare stakeholders in primary practice, suppliers, pediatric centres, and adult centres.

The issue of age of transfer is geographically and developmentally dependent, but has a large impact on hospital and insurance policies. This age varies between 18 and 26 years in the United States, 18 years in Canada, and 16 years in the United Kingdom/Ireland. What has been clearly demonstrated by those using transitional readiness questionnaires, however, is that age has little to do with the ability to successfully transition over time to adult hospitals, and what is more pertinent is the process of how this takes place. Moreover, some patients with developmental or cognitive disabilities may never reach all the milestones necessary for full transition to independent adult care. Bower *et al.*, on behalf of the International Children's Continence Society, emphasized the importance of attempting to begin the transition process at an early age. This presents a difficult challenge for both single-payer public healthcare systems (United Kingdom, Canada) and multi-payer systems (United States) in securing adequate funding for adolescents with multidisciplinary needs to allow for uninterrupted and developmentally appropriate services from adolescence to early adulthood.[12,124] One such systems model to allow for early and sustained transition to adult clinics has been described by Lewis *et al.*, in which they describe a four-stage REACH model for the transition clinic (T1-T4), with the first stage of transition beginning at approximately 12 years old and active transitioning occurring at approximately 15 or 16 years old, depending on an adequate readiness score. Clinics in both

pediatric and adult hospitals take an active role, with shared costs to each system, to achieve a seamless transition.[179] The appeal of this program is the mutual contribution of resources to the effort. This has been a critical impediment to transition in nonsocialized medical systems.

Regardless of which model is used, there is a significant role in the success of transition played by hospital and insurance systems, and a paucity of available outcomes data. The issue of insurance is challenging, as different models exist depending on national and local differences in payment models and changing systems as they evolve through time. In addition, the costs and potential savings, both economic and social, of multidisciplinary healthcare teams and transition are not defined, and therefore no economic analyses can be performed at this time. Further data relating to the roles of hospitals and insurance as facilitators and barriers to successful transition, as well as better characterization of the cost of failed transition, are required to adequately develop a unifying framework and, in some cases, justify the existence of these programs.

1.7 Summary of Recommendations

1.1.2.1 Recommendation for lower urinary tract function

- Any change to urologic function (eg, worsened incontinence, escalating infections, stones, new hydronephrosis) that occurs during periadolescence merits a thorough investigation, including a detailed history and appropriate diagnostic testing.

1.1.5.1 Recommendations for sexual/reproductive function

- Men with a history of genital surgery in childhood are at a high risk for sexual dysfunction and cosmetic dissatisfaction as they become sexually mature. Urologic follow-up through puberty and into adult life is warranted and appropriate treatment or referral to sexual health or fertility experts offered when relevant.
- Appropriate and early referral to reproductive/endocrine gynecologists should be considered for young women at risk for fertility impairment and with the congenital conditions discussed herein.
- Appropriate and early referral to maternal fetal medicine specialists should be considered for young women with the congenital conditions discussed herein.

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C2

Challenges to the Paradigm in Pediatric Practice Based on the Long-Term View

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Committee 2

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Challenges to the Paradigm in Pediatric Practice Based on the Long-Term View

2.1 Standardization of Disease Classification and Practice

A standardized classification of congenital urologic conditions facilitates their management; it offers consistent care for patients and readily comparable communication between care providers. For example, in the case of antenatal hydronephrosis, the application of either the Society for Fetal Urology (SFU) or Urinary Tract Dilatation (UTD) classification system allows for standardized radiologic reporting and objective assessment of improvement or worsening. However, many conditions encountered in pediatric urology are rare, with varied management and presentation, making consensus and standardization challenging. This leads to the creation of many classifications systems, based on either anatomy, function, or specific parameters. Herein, we will review the principal classifications of diseases frequently seen in pediatric urology that affect health and healthcare delivery throughout life.

2.1.1 Neuropathic bladder dysfunction

Neuromuscular dysfunction of the lower urinary tract (LUT) in pediatric patients can be divided into 2 categories[1]: congenital or acquired. The most common cause of neuropathic bladder is a congenital neural tube defect involving the spinal cord (spina bifida, or SB). The incidence of neural tube defects varies widely within Europe, with an estimated incidence of 9.1:10,000 reported in a recent publication of European Surveillance of Congenital Anomalies[2] (EUROCAT). The incidence per 10,000 births has been estimated to be 0.5 in the United States and around 3.0 in England[3,4]; however, another analysis[5] found the rate in the United States to be 2.9 to 3.4 per 10,000 births. SB is typically subclassified according to the level of the spinal defect (cervical, thoracic, lumbar, lumbosacral, or sacral). In the most common and most severe form of SB—open neural tube defect or myelomeningocele—it is important to remember that the level of the bony vertebral deficit often does not predict the level of neurologic deficit.[6] Bladder function remains variable and cannot be predicted based on spinal anatomy and neurologic examination of the lower limbs alone. Other congenital forms of neuropathic bladder dysfunction (NBD) include closed and occult forms of neural tube defects, sacral agenesis (caudal regression syndrome), and anorectal malformations (ARMs). The acquired etiologies include extensive pelvic surgery or pelvic radiation, central nervous system disease, and spinal cord insults. The International Children's Continence Society[7] (ICCS) has highlighted the importance of a clear nomenclature for the etiology of the NBD. The initial diagnostic evaluation and follow-up are based on many factors, including the NBD underlying causes.[8]

The bladder has 2 main functions: storage and elimination of urine. NBD may result in failure of proper storage, emptying, or both. Categorization according to the abnormality of bladder function may be beneficial for medical and surgical management. For example, patients experiencing issues with bladder storage may have low detrusor compliance, low bladder capacity, detrusor overactivity, or low bladder outlet resistance. Poor emptying may result from inadequate bladder contractions or detrusor-sphincter dyssynergia. A thorough history can help differentiate the symptomatology between the voiding or storage phases of the bladder. In 2016, the ICCS[7] published a guideline for standardization of terminology of LUT function in pediatric patients. Storage symptoms include

increased (>8 times/day) or decreased (<3 times/day) voiding frequency, incontinence, urgency, and nocturia. Hesitancy, straining, weak stream, intermittency, and dysuria are terms used to describe voiding symptoms. While symptoms are important indicators, they can be misleading in the absence of urodynamic assessment.

Urodynamic evaluation of the LUT can be classified as either noninvasive or invasive.[7] Examples of noninvasive tests are bladder diaries, 4-hour voiding observations, and uroflowmetry. Invasive urodynamic studies (UDS) (cystometry with or without fluoroscopy [videourodynamics]) are usually conducted when symptoms, noninvasive studies, or both raise suspicion for severe or neuropathic detrusor-sphincter dyssynergia, obstruction, genitourinary anomalies, or significant vesicoureteral reflux (VUR) of unknown cause. In specific situations, especially in patients with SB, urodynamic evaluation will provide an important assessment of LUT function and will guide management. In many centres, UDS are performed in infancy as a baseline and with some regularity to identify those with a "hostile" bladder with high storage pressures. The ICCS[9] published a standardized report on UDS in 2015 to streamline documentation and measurements of UDS.

2.1.2 Bladder outlet obstruction

Posterior urethral valves (PUV) is the most common cause of bladder outlet obstruction in male fetuses and infants, with an estimated incidence of 1:7,000 to 1:8,000 live births.[10,11] These valvelike leaflets in the posterior urethra were first classified by Young and colleagues (1919)[12] into 3 types, based on the anatomy of 12 cases. This classification is an anatomic nomenclature only and does not predict outcomes:

- Type 1 (most common) consists of 2 mucosal folds arising from the verumontanum and extending anteriorly with fusion in the midline, proximal to the external striated urethral sphincter.
- Type 2 is no longer considered pathologic, but a normal anatomical variant described as leaflets arising from the verumontanum and extending posteriorly and superiorly to the bladder neck.
- Type 3 (referred as Cobb collar, Moormann ring, or congenital stricture) is described as an obstructing ring with a small opening in the centre, located below the verumontanum.

Young's classification was refuted in 1992 by Dewan *et al.*,[13] who concluded that most congenital posterior urethral obstructions were anatomically similar. They proposed the term "congenital obstructing posterior urethral membrane" (COPUM) to describe this common morphological diagnosis with obstruction of the posterior urethra. The authors also pointed out that the type 1 valves are probably the result of urethral instrumentation of type 3 membranes.

Prune belly syndrome (PBS), also known as Eagle-Barrett syndrome, is a rare disorder that presents with a constellation of anomalies. The incidence is estimated around 3.8 per 100,000 live births.[14] The classic triad of findings associated with PBS consists of deficiency of abdominal musculature, bilateral intra-abdominal testicles, and urinary tract abnormalities. There is a wide spectrum of clinical presentation with variable severity. Due to this variability and spectrum of severity associated with PBS, Woodard[15] described 3 major categories of presentation in the neonatal period. Category I

includes severe urinary tract obstruction or renal dysplasia associated with antenatal oligohydramnios. These are the most severely affected infants, who typically have pulmonary hypoplasia and Potter features, and usually do not survive beyond the first few days of life as a result of pulmonary complications or renal failure. Newborns in category II present with the full PBS spectrum; however, renal dysplasia tends to be unilateral or of much lower severity; renal function may either stabilize or eventually progress to renal failure, as noted in 23% of boys in a long-term analysis.[16] As such, the treatment of these neonates remains controversial.[17-19] The primary management goals, as with all congenital uropathies, include preservation of renal function and prevention of urinary tract infections (UTIs). Finally, infants in category III have incomplete or mild features of the described triad. They have no evidence of pulmonary hypoplasia or renal dysplasia. Renal function is usually stable with mild to moderate dilation of the urinary tract. Surgical intervention on the urinary tract remains controversial and is restricted to patients with worsening renal function or recurrent UTI.[20]

2.1.3 Bladder exstrophy-epispadias complex, including classic bladder exstrophy, variants, and cloacal exstrophy

Classic bladder exstrophy (CBE) is a term often used synonymously with bladder exstrophy-epispadias complex (BEEC). Clinically, there appears to be a spectrum ranging from primary epispadias as an isolated condition (affecting the urethra, and, in more severe forms, the bladder neck) to CBE and through to the multisystem defects of cloacal exstrophy (CE). In fact, there are no clear data to explain whether these are isolated disorders with anatomical links or whether this is truly a spectrum of disease with a common embryological basis.

CBE has been reported to occur in 1:45,000 to 1:60,000 births, with a male:female ratio of 2.3 to 6:1.[5, 21] Isolated epispadias also has a higher male incidence of 1:117,000 compared to 1:484,000 in females.[21] CE is the rarest form of BEEC, with the incidence noted to be in 1:200,000 to 1:400,000 births.[21]

CBE is a severe pelvic anomaly that may affect the anterior abdominal wall, bladder, urethra, genitalia, pelvic bones, and, in some cases, the rectum and anus. Skeletal issues stem from pubic diastasis, leading to an increased distance between the hips, waddling gait, and outward rotation of the lower limbs. Premature rupture of the cloacal membrane is believed to lead to abdominal wall defects and commonly associated indirect inguinal hernias. The perineum is short, with all structures (urethra, vagina [in females], and anus) being displaced anteriorly. Colorectal anomalies, such as imperforate anus, rectal stenosis, and congenital rectal prolapse, have been associated with CBE and may represent a spectrum between CBE and CE, its most severe form. Males with CBE can present with marked congenital deficiency of anterior corporal tissue, leading to a short penis. In females, the vagina is shorter than normal, and the orifice is frequently stenotic and (as described above) displaced anteriorly. The cervix lies near the introitus in the anterior vaginal wall and the clitoris is bifid. At birth, the upper urinary tract is usually normal, with the exception of often incompetent ureteral orifices that may result in VUR after bladder closure.

CE may also be referred to as omphalocele, exstrophy, imperforate anus and spinal (OEIS) defects, due to associated neurospinal defects, hindgut deficiency, and omphalocele.[22] These additional features make it a more complex condition to treat both initially and in the long term. Gastrointestinal tract anomalies occur in all CE patients, and at birth, it is common to find a foreshortened gut or cecum

located between 2 exstrophied hemibladders. Complete phallic or clitoral separation, an even wider pubic diastasis, omphalocele, and imperforate anus are part of the constellation of CE anomalies. Müllerian anomalies are the norm, with complete separation of the müllerian ductal structures, usually presenting as uterine duplication, vaginal duplication, or both, or vaginal agenesis in some females. Renal anomalies, such as pelvic kidneys and renal agenesis, are also more common in CE than in CBE.

In 1987, Manzoni *et al.*[23] published a classification that allowed patients with CE complex to be categorized in 2 groups based upon bowel–bladder relationship, with 3 subgroups in each (**Table 2-1**):

TABLE 2-1 Cloacal Exstrophy Complex Classification

Type 1 (classic)	A	Hemibladders confluent cranial to bowel
	B	Hemibladders lateral to bowel
	C	Hemibladders confluent caudal to bowel
Type II (variant)	A	Bladder variation
	B	Bowel variation 1. Distal bowel anomaly 2. Fistulous communication without bowel anomaly
	C	Mixed forms (bladder and bowel variation)

Adapted from: Manzoni GA, Ransley PG, Hurwitz RS. Cloacal exstrophy and cloacal exstrophy variants: a proposed system of classification. *J Urol.* 1987;138(4 Pt 2):1065–1068.

The goal of this classification system was to facilitate and standardize documentation and communications. The coding and systematic classification that the authors used help distinguish the classic form of CE from the other variants.

BEEC may also be divided in 2 groups: classic or typical forms (epispadias, CBE, and CE) and atypical forms (duplicated exstrophy, covered exstrophy, and pseudoexstrophy). Many variants of CBE have been described, and the term pseudoexstrophy indicates the musculoskeletal defect usually found in CBE in the absence of urinary tract anomalies.[24] A superior vesical fissure presents with the musculoskeletal defects of CBE, but the patient has a congenital vesicocutaneous fistula similar in appearance to a vesicostomy. A covered exstrophy is similar to CBE, except for persistence of the cloacal membrane without later rupture.[25] Epispadias is addressed in **Section 2.1.6**.

2.1.4 Cloacal and anorectal malformations

Persistent cloacal malformations and ARMs represent a wide spectrum of defects, ranging from mild anal anomalies to complex cloacal malformations. The incidence ranges from 1:3,000 births for imperforate anus to 1:40,000 to 1:50,000 for cloacal anomalies.[5,26] The first classification for ARM was reported by Heister[27] in 1749. With the advancement in the understanding of ARM, many classification systems have been created since the early 1980s, including the Wingspread classification,[28] which was one of the most commonly used until 2005. This classification distinguishes among low,

intermediate, and high ARM, based on the levator ani muscle, and also includes rare malformations. Popularization of the posterior sagittal surgical approach led to the realization that the site of the fistula had a significant impact on long-term outcomes. Thus, in 1995, Pena[29] proposed a new classification to introduce anomalies that were not included in the Wingspread classification and to highlight the importance of the fistula. Comparing long-term outcomes from ARM literature became challenging due to the variation in the follow-up criteria. In 2005,[30,31] the Krickenbeck classification was introduced to standardize the methodology to allow comparison of follow-up and incorporation of elements from the Pena and Wingspread classifications. As a result, 3 categories were included: diagnostic (site of fistula and presence of rectal/anal stenosis); surgical procedures performed; and functional outcome (degree of soiling and constipation). Cloacal anomalies can impact the urological and the gynecological systems, and more authors suggest reporting these outcomes as well.

Finally, it has been pointed out by Pena *et al.*[32] that the length of the common channel can also have a significant impact on surgery and outcomes. Patients with a channel of greater than 3 cm have a higher incidence of urological anomalies, often require a more complex surgery, and have a higher risk of poor functional results when compared to patients with a channel of 3 cm or less.

2.1.5 Differences of sexual development

Differences of sexual development (DSD) encompass a broad spectrum of endocrinopathic as well as structural anomalies that can result in ambiguous genitalia at birth. Because definitions vary, it is difficult to pin down a specific incidence, but it may be in the order of 1:15,000 to 1:18,000 births.[5,26] There are multiple classifications to systematically categorize the possible causes of DSD, previously commonly referred to as intersex disorders. This is beyond the scope of this chapter. The classification that was published following the consensus statement on management of intersex disorders[33] ("Chicago Consensus") introduces more contemporary terminology, as there was dissatisfaction with previous nomenclature used in the historical classifications. The classification is divided into 3 categories: sex chromosome anomalies, XX disorders, and XY disorders. The last 2 categories are further subdivided into primary disorder of gonadal development, disorder of sex steroids from a morphologically normal gonad, or other.

2.1.6 Urethral anomalies

Hypospadias is the most common congenital anomaly of the penis, occurring in 1:300 males,[34] and there are several classification systems used during clinical or surgical assessment. The most common hypospadias classification was published in 1996 by Duckett,[35] and defects are described according to the position of the meatus after release/correction of penile curvature (**Table 2-2**). Meatal location can be classified as anterior (glanular, subcoronal, distal penile), middle (midshaft), or posterior (proximal penile, penoscrotal, scrotal, or perineal). However, due to the complexity of hypospadias, many surgeons believe that more than 1 measurable or observable parameter is needed to accurately classify this condition.[36,37] Penile curvature, scrotal transposition, dysplastic urethra, and abnormal foreskin can all influence the degree of severity, thus making the reconstruction more complex and challenging. Recently, Orkiszewski[37] proposed a new classification based on the location of the separation of the corpus spongiosum relative to pelvis bone structures after complete mobilization of skin flaps. While the classification remains nominally similar to Duckett's, the proposed advantages include

elimination of ambiguity in patients with ventral curvature and continued reliability in patients with perineal abnormalities. Hadidi[35] suggested that preoperative assessment should indicate the site of the meatus and the presence or absence of ventral curvature. An intra-operative assessment should also be carried out describing the location of the meatus after correction of the ventral curvature. These 2 assessments, alongside a description of the ventral curvature, condition of the prepuce, glans cleft, urethral plate width, penile rotation, and scrotal transposition are designed to standardize the classification of hypospadias.

The glans-urethral meatus-shaft (GMS) classification was developed to standardize the evaluation of hypospadias severity. Three components are assessed: glans (G), meatus (M) and penile shaft (S). Each component is "scored" on a scale of 1 to 4, with 4 being the most unfavourable characteristic. The sum of each value is calculated to determine a total GMS score. While the score was shown to have a high inter-observer reliability and to correlate with the risk of surgical complications, it has been criticized for its subjective component.[38] The GUMS score is a further modification of the GMS, adding urethral plate quality (U). To assess the postoperative outcomes and cosmetic result of the repair, several tools are available. The Hypospadias Objective Penile Evaluation (HOPE) score, Pediatric Penile Perception Scoring (PPPS), Hypospadias Objective Scoring Evaluation (HOSE), and Hadidi score are examples that can be used by both clinicians and patients or their parents.[39] However, most of these tools have been criticized for lack of preoperative assessment, their subjectivity, or being too time-consuming to complete. To date, there remains a lack of consensus regarding which of these systems and tools are most valuable in the assessment of preoperative hypospadias characteristics and postoperative outcomes.

TABLE 2-2 Various Classifications for Hypospadias Based on Meatal Location

Smith 1938	Browne 1938	Schaefer 1959	Avellan 1975	Duckett 1996
First degree	Glanular	Glanular	Glanular	Glanular
Second degree	Subcoronal Midshaft	Penile	Penile	Subcoronal Distal penile Midshaft
Third degree	Penoscrotal Midscrotal Perineal	Perineal	Penoperineal Perineal Perineal without bulb	Proximal penile Penoscrotal Scrotal Perineal

Adapted from: Hadidi AT, Azmy AF. *Hypospadias Surgery: An Illustrated Guide.* Berlin, Springer Verlag, 2004.

As previously noted, epispadias is a rare congenital anomaly of the penis and bladder neck that can occur in isolation but is more commonly associated with other anomalies that are part of the BEEC (CBE and CE). The urethra is placed dorsally, and commonly has decreased anterior corporal length and dorsal penile curvature. In more severe (proximal) epispadias, bladder neck incompetence is present and can impact urinary continence. There is no formal classification of the isolated epispadias. In males, the terms balanitic or glanular, penile, and complete or penopubic epispadias will sometimes be used to describe the location of the meatus.[22] In females, Davis[40] described 3 degrees

of epispadias. In the mildest degree, the meatus is patulous; in the intermediate degree, the urethra is open dorsally on most of its length; in the most severe degree, the entire urethra and the sphincter are involved.

2.1.7 Cryptorchidism

The incidence of cryptorchidism at birth varies based on birth weight and gestational age and decreases in the first year of life due to spontaneous descent of the testes that occurs in most boys. Approximately 1% to 2% of boys have cryptorchidism at 1 year of age, and the prevalence can increase in older boys due to the entity of delayed testicular ascent.[41] There have been many attempts to create a classification for cryptorchidism to facilitate research, direct management decisions, and make prognostic predictions. The Schoorl classification[42] divides undescended testes (UDT) into 4 categories: retractile, subcutaneous, cryptorchid, and ectopic. Beltrán-Brown *et al.*[43] also suggested a new clinical classification for testes found in the inguinal canal, based on their experience with 1,010 orchidopexies and on testicular location, size, and mobility. Categories include: I (lower third), II (middle third), and III (upper third) of the inguinal canal; A (normal size), B (30% smaller than normal), and C (>30% reduction from the normal); and fixed vs movable. Orchidopexy results were found to be poorest in patients with greater than a 30% decrease in testicular size. They conclude that patients with size A testes can wait until 1 to 2 years of age before undergoing surgery to allow sufficient time to exclude retractile testicles; however, surgery is recommended as early as 6 months old for patients with testicular sizes B and C. Whitaker[44] described a system which classifies UDT as either palpable or nonpalpable and then further subclassified according to their position during simple palpation, manipulation, or surgery. Similarly, in 1993, Kaplan[45] published a nomenclature of cryptorchidism based on the location of the testicle. While there has been a gain in knowledge from all of these publications, we also appreciate that in most clinic settings differentiation between unilateral vs bilateral and palpable vs nonpalpable testes is typically sufficient for determination of the appropriate management. When surgery is indicated, palpable testicles will be managed through inguinal or scrotal incisions, which is decided by the surgeon based on testicular position, surgical experience, and preferences.

2.1.8 Recommendations

- Classification schemas for various congenital urological anomalies are variably standardized based on anatomy, surgical aspects, and functional outcomes, and change frequently. It is recommended that best-effort attempts are made to classify and document patient characteristics at birth and at routine intervals thereafter, based on the most current standardization schema. Tanner staging should likewise be documented when genital anomalies are characterized. The optimal classification system should have low inter-user variability and high reproducibility. **[Grade of Recommendation (GOR) C]**.

2.2 Treatment of Children and Adolescents With a History of Neuropathic Bladder and Bowel Dysfunction, or Primary Bladder Outlet Obstruction

2.2.1 Neuropathic bladder

The most common cause of neuropathic bladder and bowel dysfunction is neural tube defect, most commonly the open type of SB (myelomeningocele). In addition to neurologic and orthopedic defects, these patients suffer a variety of problems with urine storage and emptying.[46] Complications include urinary incontinence, stool incontinence, or both; UTI; urolithiasis; VUR; and deterioration of the upper urinary tracts. If not treated appropriately, upper tract damage may occur in up to 60% to 80% of patients during the first years of life, ultimately leading to renal scarring and renal failure requiring dialysis, transplantation, or both. The treating urologist must monitor the LUT for deterioration that may cause upper tract damage.[47-50]

Following birth, about 12% of neonates with SB have no sign of neuro-urological dysfunction.[51] This often changes during the first years of life and later during pubertal growth. In a systematic review, Veenboer *et al.*[52] estimated that 37% (8%–85%) of young adult patients with meningomyelocele are continent, 25% have some degree of renal damage, and 1.3% have end-stage renal disease (ESRD). The term "continence" has been defined quite variably in the literature. In only one-quarter of the reports, continence was defined as "always dry"; in others,[53] criteria include dry intervals or volume of urine lost. Additionally, patients with NBD usually have neuropathic bowel dysfunction. The National Spina Bifida Patient Registry in the United States[54] noted bladder and bowel dysfunction of in individuals with myelomeningocele aged 5 years and older in 94.6% and 88.4%, respectively, compared to 65.1% and 55.3%, respectively, of those with nonmyelomeningocele forms of SB. The associated fecal incontinence may have an even greater impact on the quality of life compared to urinary incontinence and is more closely associated with social isolation.[55]

Sexuality, while generally not an issue in childhood, becomes more important as the patient gets older and is addressed in greater detail in **Chapter 3** of this Consultation.[56]

2.2.2 Posterior urethral valves

PUV represents the most life-threatening congenital anomaly of the urinary tract during the neonatal period.[57,58] The embryology of PUV is still poorly understood, but may result from abnormal insertion of the mesonephric ducts into the fetal cloaca.[59] The impact of the PUV on upper urinary tract and LUT function appears variable.[13,60,61]

The risk for chronic kidney disease in boys with PUV can be as high as 32%.[62] One manifestation of this disease is poor urine concentrating ability, resulting in higher urine output, which can negatively influence the bladder physiology and present increased challenges for continence for a few children. The principle concern is deterioration of renal function: as noted in a recent systematic review,[62] up to 20% will develop ESRD. Risk of progression to ESRD remains throughout adult life, although it is poorly characterized.

2.2.3 Prune belly syndrome

First described by Frolich in 1839, the term prune belly syndrome (PBS) was coined by Osler[63] in 1901. Despite its initial description almost 2 centuries ago, the pathogenesis is still not well understood and multiple theories exist. Most commonly accepted is the theory of urethral obstruction causing dilatation of the upper tracts, preventing proper development of the abdominal musculature and interrupting the descent of the testes.[64,65] However, the urethra is almost always patent at birth; it is thought there is delayed canalization of the urethra.[66] A second theory[59,67] is the presence of a hypoplastic prostate, which may lead to a transient urethral obstruction. A third theory[68] cites failure of the mesodermal development. Based on those theories, there should be malformation of other organ systems, but this is not the case in most patients with PBS; consequently, great uncertainty remains about the true mechanism of PBS. However, some patients do present with nongenitourinary anomalies, including pulmonary hypoplasia or cardiovascular, gastrointestinal, or musculoskeletal malformations.[69]

Today, PBS is usually detected antenatally within the second trimester.[70] The constellation of bilateral hydroureteronephrosis and a distended thin-walled bladder (megacystis megaureter syndrome) with or without oligohydramnios raises the suspicion of PBS.[70-72] In contrast, fetuses with PUV, urethral atresia, or megacystis microcolon intestinal hypoperistalsis syndrome characteristically have a thicker bladder wall.

These diagnoses are grouped together under the term "lower urinary tract obstruction".[10,73-76] As with PUV, these patients have a higher risk for ESRD and renal transplantation. Fertility is influenced mainly by the history of intra-abdominal testes, but there are very few reports[77-80] examining sexuality and fertility in this group of patients.

2.2.4 Bladder development

2.2.4.1 Neuropathic bladder

A lesion at any level in the nervous system may cause a neuropathic bladder. The resulting lower urinary tract dysfunction (LUTD) will vary in both form and severity, and neither may relate directly to the level of the lesion.[46] Neurogenic detrusor-sphincter dysfunction is most dangerous if it causes a high pressure bladder; important manifestations may lead to incontinence and include UTI, VUR, and, most seriously, renal scarring and renal failure requiring dialysis, transplantation, or both.[81]

In patients with a neuropathic bladder, both storage and emptying of the bladder may be affected. Continence rates in adulthood are poor, with a recent study[82] suggesting 50%. The National Spina Bifida Patient Registry[83] showed 45.8% of adult patients were continent, with the majority (76.8%)

performing clean intermittent catheterization (CIC). A Danish study[82] suggested that approximately 15% of patients with SB have deteriorated renal function at a mean age of 29 years. Further renal deterioration in adult life occurs but is poorly characterized.[52]

Both bladder and sphincter function may be either overactive or underactive, and can present in 4 different combinations. History and UDS are important to understand the phenotype and help formulate disease management[84-86]: overactive sphincter and overactive bladder; overactive sphincter and underactive bladder; underactive sphincter and overactive bladder; or underactive sphincter and underactive bladder.

2.2.4.2 Posterior urethral valves

Patients with PUV may suffer marked LUTD despite valve ablation.[87] This may be masked in some; Woodhouse[61] reported that half of patients with PUV do not report or do not experience problems. Understanding has developed as patients with PUV may undergo progression of storage and voiding symptoms as they develop.[88-91] During infancy, boys, both those with and without PUV, void with high pressures.[92,93] About 75% to 80% of infants with PUV have a small thick-walled bladder, which may or may not be overactive. A high pressure bladder is more likely to lead to poor renal function.[89] Following valve ablation, most patients will show a reduction in voiding pressures. Detrusor overactivity will improve in some, with some showing increased bladder capacity.[88,91,94] Elevated postvoid residual (PVR) urine volume seems to be a lifelong feature for many patients with PUV. In the beginning, up to 75% demonstrate elevated PVR urine volume. Three years after valve ablation, up to 50% still have elevated PVR urine volume in at least 1 detailed UDS study.[91] By school age, some patients have a poorly contractile bladder and must strain to void. Progression through puberty can increase PVR urine volume as outlet resistance increases with pubertal prostatic growth, and tone and detrusor function often declines with age.[94] An underactive (or decompensated) detrusor was found in approximately one-third of patients aged 4 to 7 years of age, in two-thirds at puberty, and in up to 83% after puberty.[88,95,96] The term "valve bladder syndrome" has been used to describe the combination of poorly compliant thick-walled bladder, persistent upper tract dilatation, polyuria, and incontinence.[90,97] Koff[98] postulated that the combination of polyuria, impaired bladder sensation, and high PVR urine volume results in chronic bladder overdistension. The polyuria may be caused by a combination of congenital dysplastic kidneys and the antenatal injury affecting the concentrating ability of the renal collecting tubules.[59,99] Moreover, patients with PUV often have a hypertrophic bladder neck and, after valve ablation, this will cause a secondary functional obstruction in some, leading to further myogenic failure, as demonstrated in a small series[100] from Greece. The dilated and refluxing upper tracts may also contribute to the apparent high PVR urine volume as a result of secondary bladder filling.[98,101,102]

Boys with a history of PUV may be delayed in achieving urinary continence.[103-106] They have impaired bladder sensation, which appears to affect toilet training.[98,101,102] In boys 12 to 18 years of age, 71% of 21 patients were continent, whereas in those under age 12, only 54% were continent.[106] A history of antenatal or neonatal diagnosis with or without high serum creatinine was demonstrably associated with delayed achievement of continence.[104] There is controversy regarding the effect of early vesicostomy or high diversion (ureterostomies) on ultimate bladder function. Some authors[107-112] showed minimal or no effect; others showed reduced bladder capacity and bladder compliance over time,

requiring later bladder augmentation in 25% to 42%. Patients with continuing deterioration of the upper urinary tract despite adequate bladder drainage may receive a high diversion; therefore, this may be a group that has a worse prognosis.

2.2.4.3 Prune belly syndrome

In contrast to patients with PUV or neuropathic bladder, the dilated urinary tract in PBS is a low-pressure system. Up to 75% of the patients have VUR.[113] UDS demonstrate that the bladder is typically compliant and overactivity is rare. Significant PVR urine volume results from poor detrusor contraction, in combination with a high incidence of VUR (secondary refilling).[114]

2.2.5 Treatment and outcome

The initial goals of treatment concerning the urinary tract are preservation or improvement of renal function and prevention of UTIs. Later in childhood, urinary and fecal continence become important.

2.2.5.1 Neuropathic bladder

As a result of LUTD, most patients with SB need to empty their bladders by CIC. Starting CIC soon after birth leads to a reduction in renal complications and the need for bladder augmentation.[115-117] The National Spina Bifida Patient Registry[83] recently reported that 76% of adult patients with SB perform CIC. Detrusor overactivity is primarily treated with anticholinergic medication.[118,119] In adulthood, it is estimated that approximately half of these patients need anticholinergics.[83] Mirabegron, a ß3-agonist, may be an alternative or additive agent and may also be effective in patients with neurogenic bladders. However, there is a more limited experience with this drug in congenital neuropathic bladder and it has not been approved for use in children in many countries.[120-124] Alongside early CIC, early prophylactic treatment with anticholinergics has been shown to be important in the reduction of bladder pressures and therefore of long-term benefit.[115,117,125]

For bladders refractory to anticholinergics, the use of intravesical injection of onabotulinumtoxin A is an approved treatment option in adults and in children (in some healthcare systems).[126,127] A study[128] of children under age 16 years with SB at 6 French centres showed clinical and urodynamic success in 66% and 34%, respectively; the effect wore off over time with a median interval between injections of 11 months. The effectiveness of onabotulinumtoxin A appears to be greater in patients with bladders with detrusor overactivity versus those with poor compliance.[129,130] In patients with SB, all forms of neuromodulation, including intravesical electrical stimulation of the bladder,[133-135] sacral nerve stimulation,[136,137] transcutaneous neuromodulation,[138] and intradural somatic-to-autonomic nerve anastomosis[139,140] are considered experimental and should be used only in clinical trials, as there are little or no published data to support current clinical use. Urethral dilatation has been reported by 2 centres[141-144] as a safe and effective method to lower the pop-off pressure by lowering the detrusor leak point pressure in highly selected patients (mostly female). Vesicostomy—preferably a Blocksom stoma[145]—is a temporary solution in infants, if the parents are noncompliant with or otherwise unable to perform CIC.[146-148] The expansion of treatments to include onabotulinumtoxin A has improved the choice for patients but, should these fail, bladder augmentation or urinary diversion using ileal segments, colonic segments, or both should be considered.[149,150] Augmentation cystoplasty using bowel segments serve to increase bladder capacity, reduce storage pressure, and therefore protect the upper urinary tract. Symptomatically, the patient will expect an improvement in urinary

continence.[151,152] A continent cutaneous catheterizable channel (Mitrofanoff or Monti procedure) is an option for patients who are not able to perform urethral CIC. Surgical complications and revision rates in these patients are significant (see **Chapter 4** and **Chapter 5**).

In certain rare cases where there is a redundant dilated ureter (i.e., from a nonfunctioning kidney), ureterocystoplasty is an option. If this is possible, it will avoid some of the adverse aspects of enterocystoplasty. Careful patient selection is key, as those without VUR and a preoperative ureteral diameter of 1.5 cm or greater, or those without VUR and only mildly decreased compliance, had better results; the need for subsequent re-augmentation rate can reach 73%.[153,154] Auto-augmentation with partial detrusorectomy or detrusor myotomy are options, but in very select cases; they tend to belong more in the realm of pediatric urology rather than adolescent or adult medicine.[155-158] Patients need to be carefully selected, as data[159,160] show that only those with preoperative bladder capacities of 75% to 80% of the expected volume have a reasonable chance of success. A modification of auto-augmentation by seromuscular cystoplasty has also not proven to be as successful as standard enterocystoplasty.[161] The same is true for a tissue-engineered approach to bladder augmentation, which is still limited to the research arena.[162,163]

Continent catheterizable channels can be sited either at the umbilicus or lower abdomen. The aim is to make catheterization easier if the urethra is difficult to reach or locate, for example, in a wheelchair-bound female, and more comfortable than urethral catheterization in a normally sensate male. Depending on the type of channel (i.e., appendix vs reconfigured small bowel), the revision rate in long-term studies can be as high as 50% to 60%[164,165] (see **Chapter 4**).

In patients with neurogenic sphincter weakness, medical treatment using an α-adrenergic receptor agonist is typically not effective,[166-168] and surgical therapy with a fascial sling or artificial urinary sphincter may be required to gain continence.[169-171] The use of synthetic slings in girls with neuropathic bladder who require CIC through the urethra have had poor outcomes and should not be used.[172] In males, an artificial sling may be an option[173]; however, mid- and long-term results are lacking. Artificial urinary sphincters can achieve continence rates of up to 85% in select patients.[174-177] Postpubertal patients who can void spontaneously are good candidates, if they have good manual dexterity. In select patients, CIC through an artificial sphincter in an augmented bladder is possible.[178] Erosion rates can be up to 29% and revision rates up to 100%, depending on the length of follow-up.[169]

In contrast to patients with bladder exstrophy, bladder neck reconstruction (BNR) in those with a neuropathic bladder is less successful.[179,180] In patients who are still incontinent after a bladder outlet procedure, bladder neck closure with a continent catheterizable stoma is possible but should be considered as a last resort. The risks of this procedure, which include complications in up to 33%, and vesicourethral and vesicovaginal fistulas in up to 15%,[181] should be considered. An increased risk of bladder stones, bladder perforation and deterioration of the upper tract function, noncompliance with CIC, and bladder irrigation may increase the risk of adverse events.[181,182]

In patients requiring surgical intervention who are not willing or able to perform CIC, an incontinent urinary diversion is a sensible option to preserve renal function, protect skin integrity, or both. In children and adolescents, the colonic conduit has shown to have fewer complications compared

to the ileal conduit,[183-186] although adult practice tends more toward the ileal conduit. Total bladder replacement is extremely rare in children and adolescents, but may be necessary in some adults due to secondary malignancies or complications with urinary diversions.

2.2.5.2 Posterior urethral valves

All patients with obstructive nephropathy will need long-term monitoring of both bladder and renal function. For a boy with PUV, much of the damage occurs *in utero* and the eventual outcome may not be possible to change despite valve resection. About 30% will develop end-stage renal failure. In the first 3 years of life, there may be a slight improvement in renal function with stabilization from age 3 to 11 years. Once puberty begins, around 50% will develop further renal failure. A glomerular filtration rate (GFR) <50 mL/min/1.73 m^2 at 1 year of age increases the likelihood of a poor renal outcome. In long-term follow-up, increasing proteinuria (>0.5 g/day) or serum creatinine is a clear predictor of renal deterioration.[61]

Overdistension of the bladder can be reduced by timed and double voiding.[96,102] In patients with elevated PVR urine volume with or without straining during micturition without anatomical obstruction, α-blockers may reduce the PVR urine volume and provide symptomatic benefit. In a study[188] of 42 patients using terazosin, mean PVR urine volume was reduced from 16 mL to 2 mL[187]; further data show tamsulosin to be effective as well. Those patients with high daytime PVR urine volume may benefit from CIC.[189-191] However, unlike children with neuropathic bladders, boys with PUV typically have normal urethral sensation and compliance with CIC is low. In such cases, a continent catheterizable channel may be necessary to facilitate bladder emptying.[191,192]

In those with detrusor overactivity, anticholinergic medication may improve bladder function,[111,193] although this comes with a low risk of reversible myogenic failure (3/37 patients in a study by Misseri *et al.*[101]) and worsening retention.[193]

Overnight catheter drainage may be beneficial for some patients. Nighttime drainage of the bladder may be helpful in stabilizing bladder and renal function, especially in those with obligatory nocturnal polyuria secondary to reduced renal concentrating ability.[98,194,195]

Bladder dysfunction ("valve bladder") is well described in this population with normal maturation.[58,104,106] Bladder functional outcomes in adult life are poorly described.[111,191,196-200] Despite the importance of UDS in the treatment of patients with valve bladder,[201,202] they are rarely reported in adults.[197]

Some patients with PUV will need to undergo augmentation to manage a low-capacity bladder, poor compliance, or both.[203-205] In patients with PUV for whom renal replacement therapy becomes necessary, bladder augmentation may need to be considered. Often bladder reconstruction can be postponed until after transplantation; with resolution of polyuria secondary to the poor concentrating ability of the native kidneys, the bladder dynamics may improve reducing the need for a cystoplasty.[206] These are clearly complex cases which must be considered on their individual merits and in consultation with a multidisciplinary team. Severe bladder dysfunction and high serum creatinine nadir (>1 mg/dL) are risk factors for later need for renal replacement therapy.[207,208] However,

renal transplantation can be performed safely and effectively.[209,210] Graft function needs to be closely monitored: urological causes of deterioration are mainly a result of valve bladder dysfunction and compliance issues.[209]

2.2.5.3 Prune belly syndrome

Ideally, intervention or instrumentation in children and adults with PBS should be kept to a minimum, in order to keep the risk of infection and bacterial colonization as low as possible. Double and timed voiding in toilet-trained children with PBS appears to have fewer complications compared to early total urinary reconstruction.[211-213] In those with incomplete emptying, CIC is an option, either through the urethra or through a surgically created channel.[114,214] In a contemporary series[114,214] of 46 boys with PBS, adequate bladder emptying was possible in most (56%–83%), with the majority requiring CIC. In those with upper urinary tract deterioration, surgery to correct VUR or massive ureteral dilation may be considered; however, high complication rates have been noted[69] with postoperative ureteral obstruction in up to 40% and persistent VUR in 30%.

Reconstruction of the abdominal wall is a matter of debate.[69] There is a wide variation in the appearance of the abdominal wall in patients with PBS. The central abdominal muscles, especially below the umbilicus, are affected and interspersed with collagen fibres. In contrast, however, the lateral peripheral abdominal wall has an almost normal appearance.[215,216] Arguments for reconstruction include improvement of the abdominal muscular tone resulting from a better quality of tissue. Secondarily, it is said[217-219] that patients experience improved bladder sensation and better efficiency of bladder emptying. For the individual patient, the cosmetic aspects may be important and should not be underestimated.[220-222] Multiple techniques of abdominal wall reconstruction have been described[218-223] with their unique advantages and disadvantages. The common principle is the advancement of well-innervated and well-vascularized muscle layers with or without excision of the central muscles and fascia. On the other hand, improvement of the abdominal wall is also possible using a conservative approach with a corset, which avoids major surgery and scars.[224,225] Due to the scarcity of outcomes reports in abdominal wall reconstruction, an evidence-based recommendation cannot be offered.

2.2.6 Stool regulation

Patients with neuropathic bladder commonly have neuropathic bowel disorders, and bowel dysfunction (constipation) may exacerbate UTI risk in patients with PUV and PBS despite the fact that the bowels are not impacted by the congenital disorder. Regular emptying of the bowels with soft stools, as well as achieving continence and independence, should be the aim, and many patients will need some form of medical or surgical intervention to achieve this. Any treatment plan should include educating patients and parents/caregivers about the importance of adequate fluid intake and an appropriately balanced diet geared toward their condition.[119] Treatment of bowel function typically follows a stepwise approach, beginning with dietary modifications and oral laxatives, progressing to rectal suppositories, digital stimulation, digital disimpaction, transanal irrigation, and, if needed, the surgical creation of an antegrade continence enema. For those who fail conservative treatment, fecal incontinence may be reduced by regular transanal irrigation (several such systems exist), which may also have a positive impact on sphincter tone and rectal volume,[226] with a low risk of complications.[227] Antegrade enemas may be needed when patients are unable to perform transanal irrigation due to anatomic (weak sphincter tone) or a body habitus that does not allow it. Surgical creation of

a Malone Antegrade Continence Enema (MACE) stoma or fluoroscopy-assisted percutaneous antegrade enema appliance (e.g., Chait) is commonly employed.[228,229] Stomal complications of infection, leakage, and stenosis occur in more than 60% of patients, and one-third require surgical revision.[230] Percutaneous placed devices represent a less invasive option to create a channel for antegrade irrigation but have the disadvantage of an external component which must be changed regularly, and peri-appliance infections can be a problem.

2.2.7 Follow-up schedule

2.2.7.1 Neuropathic bladder

European Association of Urology (EAU)/European Society for Paediatric Urology (ESPU) guidelines[81] recommend proactive treatment with CIC, with or without anticholinergic medication, starting in the first months of life.

Lifelong follow-up of these patients is required, including physical examination, renal bladder ultrasound, renal function deterioration by serum creatinine, cystatin C, or both, blood pressure, and urine dipsticks for proteinuria measurement, as well as performing UDS on a regular basis for compliant patients who have had no changes in continence or infection frequency.[81] In those who have undergone augmentation cystoplasty, blood gas analysis (pH and base excess) and serum vitamin B_{12} levels are additionally recommended. Routine annual endoscopic evaluation for detection of bladder tumours starting 10 years after augmentation is **no longer** recommended, as detection rates are poor.[231,232] Although cystoscopy is recommended, it should be performed with new-onset hematuria or bladder pain, to look for pathology. UDS after bladder augmentation are only indicated if upper tract dilatation or incontinence is not improved or if they are newly encountered at some duration after augmentation.[233]

2.2.7.2 Posterior urethral valves and prune belly syndrome

Annual lifelong follow-up is required for these 2 groups of patients. Interval of follow-up in adult life may vary depending on a patient's symptoms and severity of renal impairment. For those with worrisome bladders or with rising serum creatinine, at least annual follow-up should continue. For stable or less severely affected patients, less frequent review may be appropriate. Beside regular physical examination (including the external genitalia), the follow-up should include a reliable measure of GFR (e.g., serum creatinine), bladder function (e.g., ultrasound with PVR urine volume, uroflow studies), and upper tract evaluation (e.g., ultrasound or renal scan). UDS should be considered for changing continence, escalating UTIs, new hydronephrosis, or worsening GFR. Additionally, in such circumstances, treatment to improve bladder emptying first by α-blockers, and, if insufficient, by CIC, with or without overnight drainage, should be considered. In patients with bladder augmentation, a continent catheterizable channel, or transplantation, the follow-up is the same as for the patients with a neuropathic bladder.

2.2.8 Conclusions

This review of patients with complex congenital anomalies affecting the urogenital system demonstrate that these patients need lifelong follow-up by someone who is familiar with the problems arising from these congenital malformations. This includes regular assessment of the function of the upper urinary tract and LUT, as well as issues related to sexual function and fertility, when developmentally relevant.

2.2.9 Recommendations

- For all forms of congenital neurogenic bladder, lifelong follow-up is mandatory, as the function of the detrusor and the sphincter can change over time, often with silent and potentially preventable renal deterioration. **[GOR B]**.

2.3 Treatment of Children and Adolescents With Exstrophy, Cloacal/Anorectal Malformations, and Disorders of Sexual Development

The treatment of BEEC, cloacal malformations, ARMs, and disorders of sex development throughout childhood and into adulthood is important to ensure renal health and quality of life as the patient ages.

2.3.1 Bladder exstrophy-epispadias complex: evolution in disease management

The documented history of bladder exstrophy[234] dates back to 2000 BC, evidenced by a reference on an Assyrian tablet preserved in the British Museum. The techniques for management of this complex disorder have evolved tremendously in the past 200 years, involving a varied number of stages of reconstruction to improve outcomes as well as the efficiency of management. As the understanding of BEEC has developed, the importance of the muscular and bony pelvis for the successful reconstruction of the urinary tract has been further clarified.

In 1852, Syme[235] introduced urinary diversion in an exstrophy patient by anastomosing the ureters to the sigmoid colon, creating the ureterosigmoidostomy. In 1871, coverage of the open bladder surface by abdominal and scrotal skin flaps was performed by Maury.[234] In 1885, Wyman first described closure of the bladder in a neonate with exstrophy.[234] Osteotomies were first performed as part of exstrophy closure by Trendelenburg, but were fraught with serious complications.[234] Over subsequent years, techniques for approximation of the pelvis to support exstrophy closure were refined. Ureterosigmoidostomies were widely abandoned by the early 1980s[235] due to their association with malignant transformation. Long-term follow-up of these patients showed development of benign adenomatous polyps and adenocarcinoma of the colon in 5% and 3% per decade, respectively, most at the ureteroenteric anastomosis.[235-237] A number of modern approaches to the repair of bladder exstrophy are employed in the 21st century, including the modern staged repair (Gearhart and Jeffs[238]; Cendron and Mollard[239]), the complete primary repair (Grady *et al.*[240-242]), and the Kelly repair.[243-247]

Throughout childhood, patients with BEEC will undoubtedly undergo a number of reconstructive operations and often need further reconstruction in adulthood, from minor to major revisions.[236]

2.3.1.1 Time course of surgeries

In the modern staged repair of CBE, the first stage of reconstruction includes closure of the bladder, posterior urethra, abdominal wall, and bony pelvis in the newborn period, if the bladder template size and consistency are sufficient.[248] This may be done with or without bilateral innominate and

vertical iliac osteotomy. If the bladder template is too small or rigid, it will prevent a spherical closure, necessitating delay of the closure to allow for bladder growth.[249,250] The second stage involving epispadias repair in boys is usually performed between 6 and 12 months of age. Further reconstruction includes ureteric reimplantation with a continence procedure (BNR or bladder augmentation with continent stoma and bladder neck transection) when the child and family are ready, but this is rarely performed before the child is 4 to 5 years old.

The complete primary repair of exstrophy is designed to be performed as an entire reconstruction in a single stage, combining the bladder closure with epispadias repair and BNR as a single procedure.[240-242] Over the past few years, there has been a movement to performing complete primary repair when the child is beyond the newborn period.

The Kelly technique[243,245-247] for exstrophy closure involves an initial closure without osteotomy, followed by radical soft tissue mobilization prior to urethral repair. At birth, closure of the bladder dome and inguinal hernia repair is performed. Between 3 and 6 months of age, the proximal urethra is reconstructed and soft tissue, including the pelvic floor muscles, is radically mobilized to create a sphincteric complex. In males, penile lengthening is also performed at this time and a penoscrotal urethrostomy is fashioned. Surgery to relocate the urethral meatus from its hypospadiac position to the glans is performed at approximately 3 years of age. When evaluating the patient who has had urinary tract reconstruction, it is important to understand the closure techniques used, if those records are obtainable.

2.3.1.2 Evaluation and follow-up

The goals of reconstruction of the urinary tract include the preservation of renal function, creation of urinary continence, and genitalia that allow for sexual function. The most important aspect of caring for the patient who has had complex urinary tract reconstruction as a child is ensuring the preservation of renal function. Through refinements in surgical techniques over time, the rates of renal failure have decreased.[251]

Continued follow-up through childhood into adolescence and adulthood is crucial to ensure preservation of renal function and quality of life. There are no set guidelines for follow-up, but most experts agree[251] that yearly determination of renal function with serum blood urea nitrogen and creatinine, as well as renal and bladder sonography, in the otherwise asymptomatic healthy patient is needed. Further imaging and evaluation are indicated by abnormal findings in these modalities.

Urinary continence substantially impacts quality of life for these patients. Regular assessment of continence via urethra, stoma (when present), or both, as well as length of dry interval and diurnal variability, is imperative. Various studies[236,238,252,253] discuss social continence as defined as the ability to stay dry for 3 hours between voids. Others define continence independent of their voiding status (i.e., patient is dry because they perform CIC). Some patients require bladder neck procedures such as a BNR or a bladder neck sling to create outlet resistance while allowing them to void per urethra. Others are unable to empty their bladders sufficiently by voiding and require CIC for dryness. Another group of patients will need bladder neck transection to achieve dryness per urethra and must rely on a strict CIC schedule for bladder emptying. Patients reporting shortening of their dry interval or new nocturnal enuresis should prompt an assessment for compliance and further investigation.

A decline in renal function may indicate nephropathy resulting from recurrent infections, obstruction at some level in the urinary tract, or reflux (primary or secondary).[251] Further evaluation with cystography, cystoscopy, urodynamics, axial imaging, or functional renal imaging with nuclear scan may be warranted, depending on the patient's anatomy and symptoms.

The need to screen for tumour formation in the reconstructed urinary tract has been controversial and is described elsewhere in this Consultation (**Chapter 4**).[254] In the adult exstrophy population alone, previous studies[255,256] have shown the risk of malignancy is 17.5%, 700 times greater than the healthy population, independent of the reconstruction status of their LUT. Transitional cell, adenocarcinoma, and squamous cell bladder cancers have all been found in patients with bladder exstrophy. Changing reconstructive techniques and possibly better counselling regarding carcinogen avoidance (e.g., tobacco) may reduce risk in future cohorts and help us better understand and implement risk reduction recommendations.[254]

Genital issues in both male and female patients with BEEC arise as they approach adolescence. In boys, the penis is shorter and wider, requiring lengthening procedures to allow them to have intercourse at an appropriate age.[257-259] Girls often require a vaginal introitoplasty to allow them to wear tampons and have intercourse (**Figures 2-1A and B**).[260] Problems with continence and concerns about sexual function can exacerbate anxiety problems, and require concurrent treatment with sexual therapists and psychologists.[261] A full review of genital and fertility challenges in adult life is provided in **Chapter 3** of this Consultation.

2.3.1.3 Complications and issues into adulthood

Many complications and issues can arise as the reconstructed child enters adolescence and adulthood. Stones, UTIs, incontinence, obstruction, and tumours are among the more common occurrences. Additionally, issues with pregnancy and delivery arise as the female with a reconstructed urinary tract enters her reproductive years.

Stones are common in the augmented bladder or neobladder, as the mucus can act as a nidus for mineral precipitation and stone formation.[262] Additionally, retained sutures in the urinary tract can also be a nidus for stone formation and should be addressed surgically. Patients should be counselled to maintain good hydration status and irrigate their bladders regularly to remove mucus. Monitoring with regular sonography and abdominal radiography (i.e., kidney, ureter, and bladder) is recommended to detect stones. Patients may require surgical interventions ranging from cystoscopy with cystolithopaxy via urethra or stoma to percutaneous or open cystolithopaxy. Upper tract stones can be managed with ureteroscopy in the orthotopic ureter, but often require percutaneous renal access if ureteral reimplantation was performed (see **Chapter 3**, **Chapter 4**, and **Chapter 5**).

Appropriate evaluation of patient compliance with bladder emptying regimen, as well as assessment of the bladder and urethra/channel, are important for disease management planning. Some children, particularly those who have undergone BNR, may have improved continence by ensuring that they empty their bladder (by voiding or CIC) on a regular basis. Bladder ultrasound or voiding cystometrogram (with or without urodynamic testing) may help in this assessment. Changes to bladder compliance should be assessed with urodynamic testing. BNR may result in decreased detrusor compliance, reduced total bladder capacity, and upper tract deterioration. When this occurs, patients

should be offered a catheterizable channel and augmentation cystoplasty. Regular imaging with renal and bladder sonography is recommended to detect upper tract changes (hydroureteronephrosis) due to bladder dysfunction. Treating physicians should evaluate patient symptoms for new or worsening UTIs and incontinence. Patients with a previously continent catheterizable channel may have suffered desussception of their channel requiring revision. Other possibilities[263,264] are formation of a vesicocutaneous or urethrocutaneous fistula, which will require repair with closure and a muscle flap.

Obstruction can occur at any level of the urinary tract. Strictures at any ureteric anastomosis can present even years after reconstruction. "Functional" obstruction, whether from a change in detrusor compliance or the existence of a "waist" in the reconstructed bladder, can necessitate reconstructive surgery with reoperative augmentation cystoplasty or reconfiguring of an existing augmentation.

Fertility is complex in this population. For females, vaginal stenosis may complicate intercourse and fertility (both conception and delivery) can be impaired.[265-268] Males typically have normal sperm production but may require assisted reproductive technology, given retrograde ejaculation or iatrogenic obstruction of their ejaculatory ducts.[265,266,269-271] In CE, sexual function in males may be impacted by neurogenic erectile and ejaculatory dysfunction.[272] There is a high incidence of müllerian anomalies in females with CE, which may substantially impact fertility potential.[273]

2.3.2 Cloacal anomalies and anorectal malformations

Patients with cloacal anomalies and ARMs have multiple reconstructive surgeries as infants and children, which can have a myriad of effects on the urinary tract. Typically, the genitourinary and gastrointestinal tracts are joined at birth and require surgical separation in infancy. Given both congenital and iatrogenic insults incurred early in life, most patients with cloacal anomalies or ARMs require lifelong monitoring and treatment for both bladder continence and compliance. Genital and fertility considerations in these patients are reviewed in detail in **Chapter 3** of this Consultation.

2.3.3 Differences of sexual development

Differences of sexual development (DSD) encompasses a broad range of diagnoses. Together with potential malignancy, these patients may face numerous issues that affect their psychology, fertility, hormonal function, cosmesis, and sexual function. The urinary tract is less likely to be involved in these patients, unless significant surgical mobilization or reconstruction of the urethra was performed. Management of the gonads must also be taken into consideration.

The risk of malignancy arising from gonadal tissue in patients with DSD depends on many factors. The presence of any Y chromosome material puts these patients at risk and, in general, the more ambiguous the genitalia in the presence of Y chromosome material and intra-abdominal gonadal location, the higher the risk.[274,275] Conditions can be grouped according to risk for malignancy. High-risk patients include those with gonadal dysgenesis with intra-abdominal gonads and gonadoblastoma locus positive, partial androgen insensitivity with intra-abdominal gonads, and those with Frasier or Denys-Drash syndrome.[274] In these patients, early gonadectomy is recommended. Moderate-risk

patients include those with streak gonads and Y chromosome, while low-risk patients include those with complete androgen insensitivity. Timing of gonadectomy in these patients is less urgent and is becoming more controversial.[274]

There is profound debate over the timing and technical aspects of surgical reconstruction in these patients. Appropriate treatment requires a multidisciplinary team approach that includes the urologist, endocrinologist, psychologist, primary care physician, other specialists, and the patient and family.

2.3.4 Recommendations

A multidisciplinary approach to the treatment of children and adolescents with BEEC, cloacal anomalies, ARMs, and DSD into adulthood is critical to ensure the preservation of renal function and the best quality of life. Patients with any of these diagnoses must be cared for in adult life by urologists who have subspecialty experience with such conditions. For females, conception and delivery may require genetic specialists, reproductive-endocrine-infertility gynecologists, and shared care with urologists and maternal fetal medicine specialists during pregnancy and delivery **[GOR C]**.

FIGURE 2–1A
A 12-Year-Old Female With Classic Bladder Exstrophy

Source: Image courtesy of Dr. Heather N. Di Carlo.

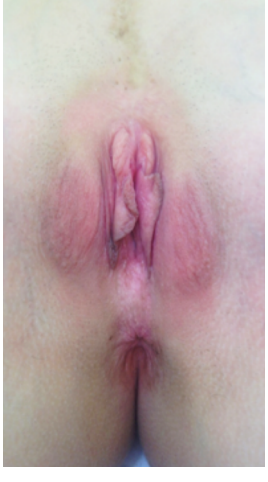
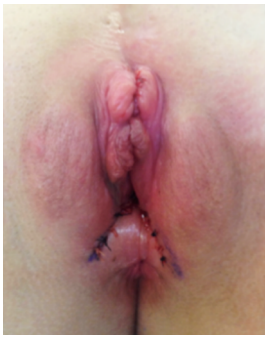


FIGURE 2–1B
She had a vaginal introitoplasty to allow her to use tampons, and, when age-appropriate, have intercourse.

Source: Image courtesy of Dr. Heather N. Di Carlo.



2.4 Embryology of Genitourinary Anomalies Affecting the Female Reproductive System

2.4.1 Development of the female reproductive system

In the absence of müllerian inhibiting substance (MIS), the müllerian ducts develop into the uterus, fallopian tube, and upper vagina. MIS also causes the wolffian ducts to regress. The müllerian ducts will progress to the lateral aspect of the wolffian ducts and continue to grow in parallel until meeting in the midline. The ducts then fuse and the membranes regress. The caudal tips of the müllerian ducts make contact with the urogenital sinus, promoting proliferation of the sinovaginal bulbs to form a vaginal plate. The proliferation increases the distance between the developing uterus and urogenital sinus. Later, the core of the bulbs degenerates and a cavity is formed between the tubercle and fused müllerian ducts. In the absence of male hormones, the indifferent external genitalia develop into the labia majora and minora and the clitoris. The genital tubercle elongates into the clitoris, while the urogenital folds develop into the labia minora and the labioscrotal swellings develop into the labia majora. It is postulated that the relative position of the wolffian duct guides migration and development of the müllerian ducts. This is likely the reason why anomalies of the müllerian duct system are commonly accompanied by anomalies in the urinary tract, as is commonly seen with cloacal anomalies.[276]

2.4.1.1 Müllerian anomalies

Müllerian anomalies result from abnormal development (vaginal atresia, absence of uterus), fusion (didelphys, septate), or migration of the müllerian ducts (persistent urogenital sinus). These anomalies can be categorized according to the organ they affect or whether they contribute to obstruction of the genital tract. They are a common congenital anomaly and affect approximately 5.5% of the female population.[277]

2.4.1.2 Transverse vaginal septum

A transverse vaginal septum typically arises from failure of vertical vaginal fusion and can be located at any level of the vagina, but most commonly affects the upper one-third of the vagina. Septa are classified in reference to the distance from the hymen[278]: low, if less than 3 cm; mid-position, if between 3 cm and 6 cm; and high, if greater than 6 cm from the hymen. In addition to the location of the septum, the thickness of the septum can vary widely. Presentation typically occurs during adolescence with progressive episodic abdominopelvic pain and primary amenorrhea as a result of obstructed menstruation.

2.4.1.3 Obstructed hemivagina ipsilateral renal agenesis

Uterine didelphys (duplicated uterus), obstructed hemivagina, and ipsilateral renal agenesis comprise OHVIRA. Renal agenesis occurs when a wolffian duct fails to develop, which influences development of the ipsilateral müllerian duct. Uterine didelphys is the result of a failed lateral fusion of the müllerian duct. The presentation of this syndrome can be misleading, and adolescents typically present with regular or irregular periods as well as episodic abdominopelvic pain.[279]

2.4.1.4 Mayer-Rokitansky-Küster-Hauser syndrome

Failure of development of the müllerian ducts, resulting in the absence of a normal uterus and vagina in a 46XX female, is known as Mayer-Rokitansky-Küster-Hauser syndrome, or vaginal agenesis. In this syndrome, girls present with primary amenorrhea and typically display a shallow vaginal pouch or dimple, with normal secondary sex characteristics. Abnormalities of the urinary tract are common and occur in 30% to 40% of cases, with concomitant skeletal anomalies occurring less commonly (10%–15%).[280]

2.4.1.5 Congenital adrenal hyperplasia

Congenital adrenal hyperplasia is a group of autosomal recessive disorders resulting from the deficiency of an enzyme required for the synthesis of cortisol. A 21-hydroxylase deficiency is the most common enzyme deficiency and accounts for 90% of cases.[281] Classic 21-hydroxylase deficiency can be divided into a "simple virilizing" subtype with normal aldosterone biosynthesis and a severe "salt-wasting" subtype with impaired aldosterone biosynthesis. A mild nonclassic form can be asymptomatic or associated with postnatal androgen excess. The 46XX fetus is exposed to systemic adrenal androgens starting at the seventh week of gestation. Virilization ensues due to excessive endogenous androgen production and results in ambiguous genitalia. Manifestations include an enlarged clitoris, rugated and fused labia majora, and a common urogenital sinus. The degree of virilization varies and can be classified by Prader stages, with stage 1 representing a phenotypic female with mild clitoromegaly and stage 5 representing a phenotypic male. The incomplete separation of the urethra and vagina during development causes a "junction" of the reproductive and urinary tract, resulting in a common channel referred to as the urogenital sinus. This junction can occur anywhere along the length of the vagina. Given that müllerian ducts develop in the absence of MIS, the uterus, upper vagina, and fallopian tubes are normally formed. There is also no development of the wolffian ducts. While external genitalia may be abnormal, internal female genitalia are often normal and fertility may be achieved. This is an important differentiating factor among all subgroups of DSD, many of which do not have natural reproductive potential and may play a role in parental decision-making regarding treatments and sex of rearing early in life.

2.4.1.6 Bladder exstrophy-epispadias complex

As discussed in **Section 2.3**, BEEC is a rare spectrum of multisystem birth defects involving the genitourinary and gastrointestinal tracts and the musculoskeletal system. Müllerian anomalies are quite common in women with cloacal anomalies, most of which are didelphys uteri, but other müllerian duct anomalies have been described.[282,283]

2.4.1.7 Cloacal exstrophy

CE, or OEIS, is a rarer and severe manifestation of the abnormal development of the cloacal membrane. This syndrome results if the cloacal membrane ruptures before the urorectal septum divides the genitourinary and gastrointestinal systems. Unlike patients with CBE, patients with CE exhibit the anteriorly exposed bladder which is bivalved with intervening bowel. Manifestations in the reproductive system include separated mons, labia, and clitoris, duplicated uterus, and anteriorly deviated vagina.[284]

2.4.2 Recommendations

- Müllerian anomalies may or may not be addressed at birth but are often addressed at the time of puberty and later on in early adult life. Involvement with experts in gynecological treatment is critical to achieving cosmetic and functional success for these women. Concurrent treatment with a urologist in situations where the urological tract is concomitantly involved is likewise critical throughout childhood and adult life **[GOR C]**.

2.5 Follow-Up of Repaired Hypospadias in Childhood and Adolescence

As boys age toward adulthood, the goals of hypospadias management remain unchanged following childhood surgical repair. The goals can be summarized as:

1. Satisfactory urinary stream with minimal to no LUT symptoms;
2. A penis of sufficient straightness and with a distally located meatus to allow satisfactory sexual function and fertility; and
3. Satisfactory self-esteem related to penile appearance

There is no agreement regarding optimal follow-up to ascertain if boys continue to meet these goals. On one hand, 70% to 90% of hypospadias cases are distal,[285,286] and both short-term and long-term surgical outcomes following distal repairs are typically very good. Therefore, some argue that universal prolonged follow-up throughout childhood is unnecessary and would overwhelm services undertaking this work. The potential detriment to self-esteem by repeated visits to the urologist may outweigh the small chance of detecting issues or complications potentially affecting urinary function, sexual function, or cosmesis. On the other hand, routine prolonged follow-up may detect issues at a younger age when there may be fewer self-esteem issues and anxiety, and may allow correction before potentially irreversible harm occurs to urinary and sexual function or psyche.

2.5.1 Onset of complications

It has been reported that 80% of urethroplasty complications occur in the first year after hypospadias repair and that prolonged follow-up would be needed in 14 boys to detect each complication subsequently encountered.[287] A series examining presentation of the most common complication—urethrocutaneous fistula—noted that 70% are diagnosed within the first year after surgery; however, the cohort did not reach the 90% and 99% detection point until 8 and 20 years later, respectively.[288] Indeed, 8% of boys presenting to Dr. Wiener's institution for repair of urethrocutaneous fistula were more than 5 years removed from initial hypospadias repair (unpublished data). These delayed fistulas are typically minor and have obvious symptoms; consequently, they do not make a compelling reason for universal prolonged follow-up.

2.5.2 Calibration of the neo-urethra

Routine calibration of the neo-urethra is preferred by some at early postoperative visits, but, given the low prevalence of postoperative urethral obstruction, it is likely only indicated in infants with suspicious obstructive voiding symptoms, small meatus, or both.[289] In older boys, calibration is best performed only under anesthesia to minimize pain and anxiety, which may negatively affect future penile perception; surgical intervention can be undertaken at the same time, if indicated.

2.5.3 Uroflowmetry

Like urethral calibration, uroflowmetry is likely not routinely indicated but can be a useful tool in boys with symptoms of obstruction, such as weak stream, prolonged voiding time, straining, elevated PVR bladder volume, and a history of UTI. Boys must be toilet trained to void volitionally. Controversies exist over technical aspects of uroflowmetry, including best data point (typically, maximum flow rate), age-related nomograms, minimal accepted voided volume, and flow curve type. It has been suggested that nearly half of boys with hypospadias repaired after toilet training have obstructive flow rates **prior** to surgery, worsening immediately after surgery, and then improving over time.[290] A Canadian group[291,292] retrospectively examined flow rates in boys with repaired distal and proximal hypospadias over a greater than 10-year period. Within both distal and proximal groups, there was no difference in flow rates between repair types, and a significant improvement was noted at puberty. In the distal group, obstructive flow patterns were noted in 60% of 2- to 7-year-old boys, but only in fewer than 10% of those older than 13 years; a similar improvement was seen in proximal repairs from obstructive patterns in 84% of 3- to 7-year-olds to fewer than 21% of those older than 13 years. The authors strongly encourage a watchful waiting approach for most boys with obstructive symptoms due to the expected improvement occurring with penile pubertal growth. Andersson *et al.*[293] noted a similar pattern for boys after distal to midshaft hypospadias repair, with only 38% having normal flow at 1 year postoperatively, but increasing to 95% at puberty. Therefore, before puberty, one must not place too much emphasis on urinary flow rate; boys with repaired hypospadias have significantly lower flow rates compared to normal controls, but these lower rates have only been correlated with elevated PVR bladder volume and not with LUT symptoms.[294]

2.5.4 Sexual function and penile perception

Until recently, no data existed regarding sexual function and penile perception in adolescents who had undergone hypospadias in early childhood. Researchers from Sweden[295] found that boys with a history of early proximal hypospadias repair had similar rates of sexual activity and age for sexual debut as controls and as those with history of distal hypospadias repair. A small percentage of those with proximal hypospadias reported erectile and ejaculatory dysfunction. Twenty-four percent of proximal cases and 16% of distal cases reported that having hypospadias negatively affected their childhood. Those with proximal hypospadias had greater concerns about penile length. Examining scholastic issues, the proximal hypospadias cohort had more tutoring in school than the distal cohort. Most of these findings corroborated earlier reports in adults with repaired hypospadias. A Dutch study[296] examining normal men and those with histories of distal and proximal hypospadias repairs noted lower scores for orgasmic and ejaculatory function in men with proximal repairs, but equivalent scores for erectile function. The proximal group had both reduced penile length when compared with controls and lower satisfaction scores for penile appearance and length compared to the distal group. Similarly, the same Swedish team[297] who studied adolescents found that men with a history of hypospadias repair had penises of smaller length and circumference, but not width, than normal controls, and that length was shorter in those with more proximal hypospadias. Penile perception scores followed a similar pattern of less satisfaction in more proximal cases of hypospadias. These data are important to share with developing teenagers when they voice concerns. An in-depth review of considerations for hypospadias in adult life can be found as **Chapter 3** in this Consultation.

2.5.5 Recommendations

- Boys with successful distal hypospadias repair can likely be discharged from the clinic 6 to 12 months postoperatively with parental education to return if the boys develop obstructive voiding symptoms or a second or abnormal stream. Due to higher risks of surgical complications as well as associated psychologic concerns, boys with proximal hypospadias need follow-up during childhood until pubertal growth is complete; in addition to a thorough history and examination, uroflowmetry may be helpful **[GOR B]**.

2.6 Follow-up of Cryptorchidism in Childhood and Adolescence

If male infants present with UDT after 6 months of age, they should undergo surgical correction by 18 months of age, according to guidelines from the American Urological Association (AUA) and the EAU/ESPU.[298,299] Following orchiopexy, most patients are followed in the short term to ensure viability and proper position of the affected testicle or testicles, as well as to rule out any postoperative complications. These patients typically do not require long-term surgical follow-up.

2.6.1 Secondary testicular ascent

Secondary ascent of previously descended testes can occur during childhood growth, particularly in retractile testes. Retractile testes do not require surgical intervention, but boys should have regular testicular examinations at annual visits with their primary care provider and be referred for surgical treatment if the testes are no longer in a satisfactory position in the scrotum.[298, 299]

2.6.2 Guideline recommendations

The AUA guidelines[298] state that "Providers should counsel boys with a history of cryptorchidism and/or monorchidism and their parents regarding potential long-term risks and provide education on infertility and cancer risk" as a clinical principle. It is unlikely that most pediatric urologists or urologic surgeons see these boys again for examination and counselling during puberty; therefore, their parents should be counselled at the postoperative visits regarding teaching of testicular self-examination during and after puberty and re-referral if testicular growth is poor.

2.6.3 Fertility

Men with a history of unilateral cryptorchidism or monorchidism have fertility similar to unaffected controls.[300,301] Conversely, formerly bilaterally cryptorchid men have at least a 3-fold increase in infertility.[302] No specific guidelines for treatment of adolescents following orchidopexy exist beyond what has been stated above, but adolescents with poor pubertal testicular growth should undergo testing of serum testosterone, gonadotropins, and inhibin B levels, and be considered for referral to endocrinology and fertility experts at an appropriate age, when indicated.

2.6.4 Testicular cancer

The risk for testicular malignancy in adults with a history of cryptorchidism is up to 1%. Recent studies[303,304] have shown that earlier orchiopexy before puberty likely reduces the risk of malignancy, but it does not lower the risk to that of normal controls. Thus, ensuring that boys are taught testicular self-examination during puberty is critically important.

2.6.5 Recommendations

- After orchiopexy, most boys do not require long-term urologic follow-up; however, parents (and the boys, if age appropriate) should be counselled regarding the increased malignant potential in testes following orchiopexy. Testicular self-examination is recommended beginning in late puberty and can be taught by the primary care provider. The primary care provider should continue to perform regular testicular examination at well child visits and refer back to the surgeon if malposition, atrophy, or poor pubertal growth is noted. Parents and patients should also be informed that unilateral cryptorchidism has not been noted to decrease fertility, but bilaterality has been associated with higher risk of infertility **[GOR B]**.

2.7 Summary of Recommendations

2.1.8 Recommendations for standardization of disease classification and practice

- Classification schemas for various congenital urological anomalies are variably standardized, based on anatomy, surgical aspects, and functional outcomes, and change frequently. It is recommended that best-effort attempts are made to classify and document patient characteristics at birth and at routine intervals thereafter, based on the most current standardization schema. Tanner staging should likewise be documented when genital anomalies are characterized. The optimal classification system should have low inter-user variability and high reproducibility **[GOR C]**.

2.2.9 Recommendations for treatment of children and adolescents with a history of neuropathic bladder and bowel dysfunction, or primary bladder outlet obstruction

- For all forms of congenital neurogenic bladder, lifelong follow-up is mandatory, as the function of the detrusor and the sphincter can change over time, often with silent and potentially preventable renal deterioration **[GOR B]**.

2.3.4 Recommendations for treatment of children and adolescents with exstrophy, cloacal/anorectal malformations, and disorders of sexual development

- A multidisciplinary approach to the treatment of children and adolescents with BEEC, cloacal anomalies, ARMs, and DSD into adulthood is critical to ensure the preservation of renal function and the best quality of life. Patients with any of these diagnoses must be cared for in adult life by urologists who have subspecialty experience with such conditions. For females, conception and delivery may require genetic specialists, reproductive-endocrine-infertility gynecologists, and shared care with urologists and maternal fetal medicine specialists during pregnancy and delivery **[GOR C]**.

2.4.2 Recommendations for embryology of genitourinary anomalies affecting the female reproductive system

- Müllerian anomalies may or may not be addressed at birth but are often addressed at the time of puberty and later on in early adult life. Involvement with experts in gynecological treatment is critical to achieving cosmetic and functional success for these women. Concurrent treatment with a urologist in situations where the urological tract is concomitantly involved is likewise critical throughout childhood and adult life **[GOR C]**.

2.5.5 Recommendations for follow-up of repaired hypospadias in childhood and adolescence

- Boys with successful distal hypospadias repair can likely be discharged from the clinic 6 to 12 months postoperatively with parental education to return if the boys develop obstructive voiding symptoms or a second or abnormal stream. Due to higher risks of surgical complications as well as associated psychologic concerns, boys with proximal hypospadias need follow-up during childhood until pubertal growth is complete; in addition to a thorough history and examination, uroflowmetry may be helpful **[GOR B]**.

2.6.5 Recommendations for follow-up of cryptorchidism in childhood and adolescence

- After orchiopexy, most boys do not require long-term urologic follow-up; however, parents (and the boys, if age appropriate) should be counselled regarding the increased malignant potential in testes following orchiopexy. Testicular self-examination is recommended beginning in late puberty and can be taught by the primary care provider. The primary care provider should continue to perform regular testicular examination at well child visits and refer back to the surgeon if malposition, atrophy, or poor pubertal growth is noted. Parents and patients should also be informed that unilateral cryptorchidism has not been noted to decrease fertility, but bilaterality has been associated with higher risk of infertility **[GOR B]**.

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C3

Sexual and Fertility Issues in Congenital Lifelong Urology Patients

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Sexual and Fertility Issues in Congenital Lifelong Urology Patients

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Sexual and Fertility Issues in Congenital Lifelong Urology Patients

3.1 Myelodysplasia

3.1.1 Introduction

As children with congenital urologic conditions survive into adulthood, their healthcare team needs to be increasingly sensitive to aspects of their development such as sexual and reproductive function. During transition, nearly all adolescents with congenital urologic conditions will express a desire to be normal. In many cases, "normal" for them means to have fecal and urinary continence, engage in a sexual relationship, and in many cases, to be fertile. Those patients unable to achieve these goals without assistance will need the guidance and support of their healthcare team to understand their condition and receive treatments allowing them to reach their full potential within the context of their physiologic or anatomic limits.

This chapter considers how congenital conditions affecting the urogenital system, including spina bifida (SB), bladder exstrophy-epispadias complex (BEEC), congenital adrenal hyperplasia (CAH), and hypospadias relate to sexual dysfunction from a medical, psychosexual, surgical, and reproductive point of view.

SB is a birth defect affecting closure of the neural tube.[1] Recent medical advances, including closure of myelomeningocele defects, shunting of hydrocephalus, and a focus on renal preservation, have reduced pediatric mortality.[2] In the adult SB population, sexual function is poorly understood and treatments for sexual dysfunction are limited.

3.1.2 Sexual function in males: medical and functional considerations

3.1.2.1 Erectile dysfunction

It has been shown[3,4] that about 75% of men with SB have erectile dysfunction (ED), although objective assessment is difficult due to lack of validated tools in this group. The International Index of Erectile Function relies on sexual activity in the preceding 4 weeks and studies[3] have shown that only 40% of men with SB had sexual intercourse in the previous month. An important factor for ED in men with SB is lack of penile sensation.[5] Patients with intact penile sensation report markedly better penile rigidity for satisfactory intercourse compared to those with diminished sensation. Nocturnal penile tumescence correlates well with sensory level[6] while the number of erections correlates with glans sensation.

Studies[4] suggest that urinary continence and intact sacral reflexes decrease risk of ED in men with SB, with 64% of men with a lesion at T10 or lower demonstrating preserved erections compared to only 14% with a lesion above T10. As expected, given the importance of lesion level, ambulant men with SB are more likely to demonstrate erectile function compared to non-ambulant men.

3.1.2.2 Treatment of erectile dysfunction

The treatment of ED is important for sexuality, self-confidence, and maintaining long-term relationships. Men with ED often respond to established therapies, including oral medications.

3.1.2.2.1 *Oral medications*

The phosphodiesterase-5 inhibitor, sildenafil, was shown to be effective in 80% cases at a dose of 50 mg in a placebo-controlled crossover trial.[7,8] Treatment increased ability to achieve and quality of erections. There were no significant side effects.[9]

3.1.2.2.2 *Surgical options*

As penile sensation is related to erectile function in men with SB, a neurosurgical solution has been investigated. In one study[10], 3 patients reported improved sensation after ilioinguinal nerve transposition to the dorsal nerve of the penis, with successful results by 15 months. This surgery (TOMAX procedure: TO MAX-imize sensation, sexuality, and quality of life) has not been routinely adopted and requires careful patient selection.[11] This may include detailed psychosexual assessment of both patient and partner, as well as a careful neurological examination to establish the level and distribution of penile sensation.

3.1.2.3 Ejaculatory function

Men with SB may also demonstrate orgasmic and ejaculatory dysfunction, which has been reported in 75% of affected patients.[5,12,13] Quality of ejaculation appears to be impaired as well. One study[14] reported that 78% of men with SB were able to ejaculate, but only 17% reported it to be forceful. Like erectile quality, ejaculatory function also correlates with the level of the lesion.[5]

3.1.2.3.1 Recommendation

- Erectile quality, penile sensation, and ability to ejaculate and achieve orgasm should all be investigated, documented, and treated in men with SB, if developmentally appropriate and desired by the patient.

3.1.3 Sexual function in females: medical and functional considerations

3.1.3.1 Menarche

Sexual maturation often occurs earlier in girls with SB.[15-22] Menarche occurs in 12% to 16% of girls with SB by age 12, compared to 0.6% in age-matched controls.

3.1.3.2 Sexual response

Little is reported regarding female sexual function in women with SB. The incidence of sexual dysfunction is not quantified and data regarding lubrication and orgasm are extrapolated from spinal cord injury women.[13,23-28] Women with SB experience additional comorbidities that may further limit sexual experience, including skeletal abnormalities, pain, and issues with bladder and bowel dysfunction.

3.1.3.3 Contraception

There are no studies examining the risks and benefits for specific birth control methods in women with SB, but one needs to avoid the known risk factors of oral contraceptives, as progesterone-only tablets may exacerbate osteoporosis and estrogen-based oral contraceptives may increase thrombotic risk.[29,30]

3.1.4 Sexual function: psychosexual considerations

It has been shown[31] that those born with congenital disabilities have impaired sexual development, purportedly due to diminished self-esteem, dependence on caregivers, and lack of privacy. Issues with relationships start at a young age. Most children with SB prefer friends who are able-bodied to those who are physically disabled.[32] In one study[33], 75% of children with SB expressed a hope to marry someday, but they preferred to marry a partner without a disability. Even at a young age, this rejection of those with similar physical and cognitive disabilities markedly impacts social isolation and promotes a poor self-image.[34]

Several studies[35,36] have shown that adolescents and young adults (AYA) with SB are concerned about dating, sexuality, and romantic relationships. This is developmentally normal for all AYAs. However, they report intense worry about the initiation of discussions about sex.[36] As such, some have reported[35] engaging in online dating and chatting to counter their physical isolation, and using social media as a means to socialize as "regular," rather than disabled. In one study[37], the majority of subjects without hydrocephalus began dating by age 18 years and by 21 in those with hydrocephalus. Patients without hydrocephalus were 3.2 times more likely to have a partner than those without.[41]

AYA with SB are less likely to have engaged in sexual activity than their age-matched peers. Analysis[38] indicated that lower levels of social adjustment in early adolescence (ages 13–14) correlated with fewer sexual partners at ages 18 to 19. Age and lesion level were found to be predictive for sexual contact.[37,39] Those older than 26 years are 2.1 times more likely to have sexual contact than those younger than 25. For each year increase in age, the odds ratio for sexual activity increased 1.1 times. Patients with a lesion at S1 or lower were 3.4 times more likely to have had sexual intercourse than patients with a higher-level lesion.[13] Smoking was also found to be a significant predictor of sexual activity in the SB population: those who smoked were 10 times more likely to be sexually active than those who did not smoke.[37] This may indicate more risk-taking behaviour.[40]

About half of individuals with SB have expressed satisfaction with their sex lives.[41] Living with a stable partner was reported to increase sexual satisfaction in men. However, there was no association with marital status and sexual satisfaction in women.[42]

Patients with SB may struggle to develop normal sexuality for a variety of reasons, including impaired self-esteem and dependence on caregivers.[43] Some may have delayed sexual development, as they are unable to develop normal peer groups as a result of urinary or fecal incontinence. There is a mistaken assumption that disabled patients, especially when wheelchair-bound, are asexual.[9] Although there are decreased sexual encounters in men with SB, their sexual desire remains intact: 80% of men with SB report normal sexual desires and fantasies and are actively interested in sexual activity.[6,12,24] Another study[3] demonstrated 40% of patients engage in sexual activity, although these patients were older and did not live with their parents. It is reported in most studies[3,41,44] that men with SB feel sexuality is important and most will engage in some sort of sexual contact.

Incontinence is also a perceived barrier to starting a relationship and a healthy sex life.[41] People with SB reported struggling with integrating their disability and their sexuality due to issues such as incontinence and lack of sensation, which impacted their perceived ability to lead a "typical" sex

life.[36] Depending on the study, continent patients were between 2 to 3.5 times more likely than incontinent patients to have a partner and 1.3 to 2.4 times more likely to be sexually active.[37,39,41] A recent study[45] showed that urinary incontinence during sex became more bothersome the more frequently it occurred, but that any degree of fecal incontinence was extremely bothersome.

Patients with SB do not believe they receive adequate sexual education and the impact of their condition on their sex life, and this directly affects their ability to have a relationship.[36] AYA with SB reported a lack of SB-specific sex education and identified it as directly impacting their ability to seek relationships.[36] In one study[41], lack of self-confidence was the most frequently cited obstacle to starting a relationship. People with SB experience sensation differently, with "normal" sensation reported in only 20% of cases.[6] This difference in sensation leads to patients with SB to undergo some discovery and develop new areas of the body to serve as erogenous zones that may stimulate arousal and lead to sexual pleasure. In men, only 41% have normal erections, with ambulant men more likely to report normal erections than those in a wheelchair.[40] Additionally, those with SB are less likely to have feelings of sexual excitement consistent with orgasm compared to the general population.[6,12,13,37,46]

Men with SB also ejaculate less frequently than the general population, and ejaculation can occur differently, often being described as more of a dribble than propulsive.[5,6,12,13,41,46] Due to all of these factors, over 91% of patients indicate that physicians should talk to patients with SB about their sexuality; however, more than half of those with SB have no recollection of such a conversation with their providers.[47]

3.1.5 Sex education

Discussing sexuality with patients can be difficult for a physician. There are multiple potential barriers, including lack of knowledge, with or without actual experience discussing sexuality; lack of resources; perceived patient discomfort; physician discomfort; and insufficient time.[48] However, patients have repeatedly expressed their desire to receive sexual education from their physicians.[36,47] Therefore, it is the physician's duty to introduce factual issues regarding sex and target this education to the needs of those who are both sexually active and to those who are not.[49] Physicians should be encouraged to ask all postpubertal patients if they have any urinary, fecal, or sexual concerns at every clinic visit to both foster patient–clinician rapport, which helps to facilitate conversations about sex[48], and alert patients that this is a safe place to discuss their questions and concerns regarding their sex and sexuality.

3.1.5.1 Recommendations

- Sex therapy specific to SB has been recommended to limit obstacles to fulfilling sexual lives. Patients with SB should be counselled on prevention of sexually transmitted diseases and pregnancy. As several patients are latex-positive, they should be informed about using latex-free condoms.

3.1.6 Fertility in males with spina bifida

Paternity rates in men with SB are lower than age-matched controls.[5,50] As expected, given observations related to erectile and ejaculatory function, paternity rates also correlate with level of lesion and ambulatory status.[5]

3.1.6.1 Treatment

Electroejaculation has been used successfully in men with SB to obtain semen. In one study, all 10 men had azoospermia, with a Sertoli-cell–only syndrome (SCOS) pattern noted on testicular biopsy. Normal testosterone production has been demonstrated in 90% of men with SB[5], so the reasons for the subfertility are not clear.[5]

There is an increased risk of neural tube defects (NTDs) in offspring of male and female patients with SB.[2] However, these data predate widespread use of folic acid. Nonetheless, patients should be counselled regarding this increased risk until more studies are available.[2]

3.1.7 Fertility and pregnancy in females with spina bifida

3.1.7.1 Pregnancy

During pregnancy, women with SB should be followed regularly by both obstetric and urological services, in order to anticipate, and avert or manage risks to both mother and baby. During this time, the rates of upper renal tract obstruction and its associated sequelae may be reviewed and treated in a timelier manner; however, serious complications in pregnancy such as sepsis still occur in this population.

Women with SB may have an exacerbation of existing pathologies as a consequence of pregnancy; for instance, kyphoscoliosis may become more pronounced, ventriculoperitoneal shunts may malfunction and require revision, and genitourinary (GU) diversions may fail.[51] Respiratory, cardiac problems, back pain, and pressure sores may also occur or worsen during pregnancy in women with SB. Some problems may persist after delivery. Women with SB should be made aware of all the potential risks to make an informed decision regarding pregnancy and mode of delivery.

3.1.7.2 Obstetric issues

Women with SB have unique challenges to overcome before and during pregnancy in addition to during childbirth. Although the number and age of women with SB becoming pregnant has increased over time, pregnancy management guidelines as yet do not exist for this patient group.[52]

During pregnancy, the management of neurogenic bladder and bowel can become an issue. These can be compounded by previous urinary and bowel diversion procedures. For example, self-catheterization through a Mitrofanoff can become more difficult during pregnancy.[30,53-56] Problems with infections and incontinence will have to be managed during pregnancy, but can result in morbidity for mother and abnormalities in the newborn.

Delivery considerations that may include fetal position; maternal pelvic and lower extremity anatomy; presence of gestational problems, like preeclampsia; prior abdominal operations; and presence of ventriculoperitoneal shunts should be made by an obstetrician experienced in high-risk deliveries, ideally in conjunction with the treating urologist.[57]

The postpartum complications may require prolonged hospitalization for women with SB. The infant can also have problems that may include hypoglycemia, jaundice, respiratory distress syndrome, and tachypnea.[29] Recurrent urinary tract infections (UTIs) during pregnancy, gestational diabetes, and preeclampsia may contribute to low birth weight and preterm infants.[58] The spontaneous abortion rate has been estimated to be about 20%; in addition, up to 11% of infants born to mothers with SB had congenital abnormalities.

3.1.7.3 Genetic and environmental risks to offspring

Studies[50,59] suggest an increased risk of NTDs in offspring of women with SB, although the risk of live births impacted by NTDs remains at baseline due to a higher miscarriage and spontaneous abortion rate, improved genetic counselling, and prenatal diagnosis for women with SB.[29] Family history of SB increases the risk of SB in siblings.[60]

Some studies[61] have focused on a variety of possible mutations involved in fetal folate metabolism, such as reduced folate carrier gene. These are postulated as factors for increasing familial incidence.[62] The nutritional deficit of folate in causing SB is proven and hence, appropriate prenatal supplementation of folic acid for women with SB is strongly advised.

Folic acid, taken orally prior to conception and during the early stages of pregnancy, plays a role in preventing NTDs, and has been associated with preventing other folic acid–sensitive congenital anomalies, such as heart defects, urinary tract anomalies, oral facial clefts, and limb defects.[63] The initial NTD translational research study[64] investigated folic acid supplementation for preventing recurrence of NTDs in a randomized, double-blind clinical trial involving 1,195 completed high-risk pregnancies in women from 33 centres. The NTD recurrence rate decreased from 3.5% in a nonsupplemented group to 1% for women randomized to the group receiving an oral 4 mg folic acid supplementation daily prior to pregnancy and throughout the remaining 6 weeks of pregnancy.

In a second randomized, controlled trial[63] for the primary prevention of NTD occurrence, the frequency of NTDs was 0 cases in 2,471 women receiving folic acid 0.8 mg per day compared with 6 cases in 2,391 women not receiving folic acid. This randomized, controlled study supported previous case-control studies providing evidence that pregnant women using multivitamins containing folic acid or dietary folic acid had a lower risk of having a child affected by an NTD than women not taking supplements.

3.1.8 Delivery

Improvements in the treatment of congenital conditions requiring bladder reconstruction have led to more women with SB surviving to childbearing age.

Cesarean section is most commonly recommended for women with BEEC or other conditions where the bladder neck and urethra have been reconstructed. The principal aim is to avoid an emergency cesarean section where appropriate urological cover may not be available, as the risks to the fetus and the mother are much higher.[115] There is no proven benefit relating to continence or damage to previous surgery. Other factors that may influence elective cesarean delivery include pelvic morphology (e.g., with caudal regression syndrome), fetal malposition, or comorbid maternal problems like preeclampsia, which is more common in the SB population. Cesarean section for women with favourable fetal and pelvic conditions who have undergone previous bladder procedures (e.g., augmentation cystoplasty), without concomitant bladder neck surgery, is more debatable. Prior pelvic and reconstructive procedures increase risk for bowel and bladder injury at delivery, and if this can be avoided safely, consideration of vaginal delivery may be prudent. Multiple pelvic adhesions are common and it is essential that the vascular pedicle supplying the reconstructed bladder is preserved. When an elective cesarean section is planned by the obstetric team, the presence of a urologist, access to adult and neonatal intensive care, appropriate equipment for abdominal laparotomy, and cross-matched blood can be prospectively prepared.

Folic acid supplementation has made a dramatic impact on reducing NTDs in the community and high-dose supplementation is recommended for any woman embarking on pregnancy who is at high risk, such as those with a personal history of NTD or a previously affected child.

3.1.8.1 Conclusion

Fertility may be impaired in women with SB, and antenatal complications and fetal loss are more frequent, requiring close obstetric and urological surveillance. Elective cesarean section is recommended for women who have had bladder neck reconstructions, have unfavourable pelvic morphology, fetal malposition, or intercurrent prenatal comorbidities. An emergency cesarean section without appropriate support leads to higher fetal and maternal mortality. Patients should be counselled about these risks before embarking on pregnancy, and when pregnant, they should be managed in a unit which can provide high-risk obstetric and urology cover.

3.1.8.2 Recommendation

- Women or their male partners with a personal NTD history or a previous NTD pregnancy are considered high risk, and they require a diet of folate-rich foods and a daily oral supplement of 4.0 mg folic acid beginning at least 3 months before conception and until 12 weeks' gestational age.

3.2 Revision Genitoplasty

BEEC is a spectrum of urogenital malformations that include epispadias in its mildest form, classic bladder exstrophy (BE), and cloacal exstrophy (CE) in its most severe form. The most commonly seen form of BEEC is classic BE, with boys being affected 3 to 4 times more than girls. Isolated epispadias is rarer and is also more common in males. CE has a prevalence of 1 in 200,000 to 1 in 400,000 live births and is more common in females.[65]

3.2.1 Psychological and developmental impact of genital anomalies

While much attention is focused on complex surgical reconstruction in BEEC performed in children, less attention has been paid to long-term issues like renal failure, urinary and fecal incontinence, fertility, and psychosocial and psychosexual development. Historically, continence and preservation of renal function in children born with BEEC has been the highest priority. Regardless of whether functional reconstruction or urinary diversion is chosen, the genital tract and lower anterior abdominal wall must be reconstructed. As children born with these abnormalities transition to adolescence and adulthood, genital appearance and function become increasingly relevant. Many adolescents with BEEC often have significant physical and psychological difficulties related to body image, self-esteem, sexuality, and sexual function due to their GU deformities, which negatively impact mental health and psychological functioning, and may interfere with their psychological and sexual development.[66,67]

Mental health is best predicted by parental relationship and genital appraisal in the 11- to 14-year-old age range, and parental relationship and urinary continence in the 15- to 20-year-old age range. Psychosocial dysfunction was predicted by fecal dysfunction in the 11- to 14-year-old age range and worries about future relationships in the 15- to 20-year-old age range.[66] Issues with relationships become more prominent in late adolescence as patients begin to experience intimate relationships for themselves. While both males and females are affected, young men appear to be more affected than young women.[68]

Men with BEEC have fewer intimate relationships than women for a variety of reasons. Some have postulated that they have greater difficulties in dealing with issues regarding their genitalia and sexual activities.[69] There is intense anxiety regarding male genitalia, including the size of the penis and the dorsal chordee with erections.[70] As men with BEEC age, incontinence management has been demonstrated to impact personal relationships.[71]

Both men and women with BEEC often report challenges in accepting their own bodies.[72] This can lead to severe depression and suicide. The rate of suicidal ideation is at least 15% in this population, more than 21.5 times that of the general population.[73] However, there are many studies that have demonstrated a good quality of life is achievable with the effective use of coping strategies.[9,74,75] Targeted programs aimed at improving self-esteem and quality of life in adolescents with BEEC are being developed. These programs are aimed at changing teens' attitudes in several psychosexual areas, such as psycho-environmental situations, body experience, areas of pleasure, medical and sexual history, motivation, and conflict areas.[72]

3.2.2 Female genitoplasty

Sexual function has been less studied in women with congenital GU anomalies, owing to the initial focus on life-saving therapies in women with complex GU anomalies and decreased overall focus on sexual outcomes for women as compared with their male counterparts. More recently, there has been renewed focus on quality of life, as children with complex GU anomalies progress into adulthood.

3.2.2.1 Bladder exstrophy and cloacal exstrophy

The initial surgical management of exstrophy is complex and focuses on patient stabilization. In terms of the reproductive system, surgery is not urgent and can be delayed. Initial management focuses on the bladder (BE), and bladder and bowel (CE). Further reconstructive surgeries are common in women with BE and CE, some of which include surgical procedures to allow for intercourse. The case series from Matthews[76] reported that 10 out of 24 women with BEEC and 4 out of 6 women with CE required further genital surgery. Castagnetti and Rubenwolf reported similar rates of genital revision in women (31%–33%), with women with BEEC requiring procedures to make the vaginal functional for intercourse (introitoplasty).[77,78]

In CE, there are several techniques for vaginoplasty, including pull-through vaginoplasty and bowel or bladder vaginoplasty.[79] Vaginal reconstruction as part of a staged bladder closure surgical management typically involves introitoplasty.[80]

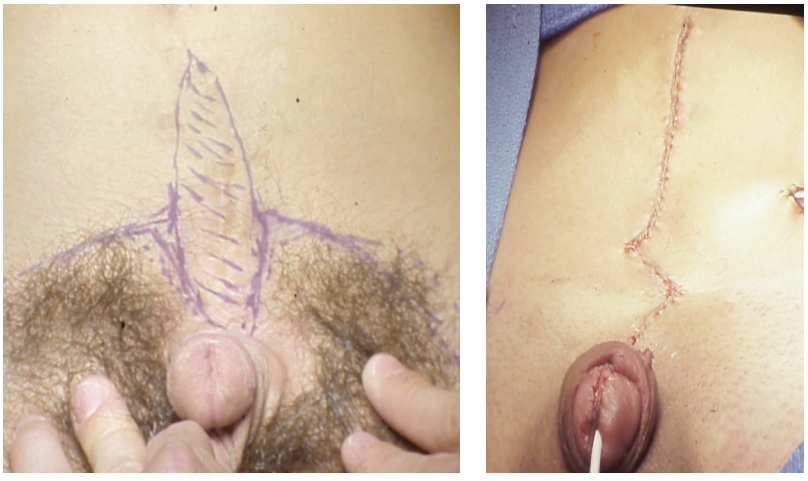
A handful of studies have evaluated sexual function in women with BE and CE. Most women with BE (90%) report sexually activity.[78,81] Two studies, both with small numbers of women with BE, compared sexual function with validated questionnaires between women with BE and healthy controls. Suominen *et al.*[82] found that women with BE had better sexual function than normal controls, while Deans *et al.*[81] reported the opposite. Dyspareunia is common in women, even in those who underwent several vaginal procedures.[76,81,83]

Some authors[84] report that women went on to have a hysterectomy for either prolapse or obstruction; however, this should be avoided whenever possible.

Patients with BE are often distressed by the fact they have scarring and a convexity in their suprapubic region. This area can be reconstructed through a variety of techniques, including the simple excision of a diamond-shaped midline depressed area followed by a longitudinal closure, preferably with Z-plasty (**Figure 3-1**); more severe scarring may require a rotational flap.[85] Bilateral groin flaps fed by superficial epigastric and superficial circumflex iliac arteries represent axial pattern flaps which can be raised without regard to the width:length ratio. Incorporation of the deep fascia in these flaps enhances vascularity and inclusion of subcutaneous fat (fascio-fatty-cutaneous) flaps provides an excellent filler for the prepubic depression.[86] The ideal timing for such cosmetic surgery is not well defined. For pubioplasty, it seems sensible to wait until pubic hair distribution is complete to make reconstruction of the skin more accurate.

FIGURE 3–1
Similar to female patients, this figure shows a monsplasty in a male patient with excision of the hairless midline area and closure, preferably by Z-plasty.

Images courtesy of Dr. Moneer Hanna.



3.2.2.2 Cloacal anomalies

Cloacal anomalies are complex anomalies with wide variations. As genital and urinary openings are common, a compressive hydrocolpos may compromise the urinary function. In those cases, immediate vaginal reconstruction used to be typically undertaken to decompress the hydrocolpos. However, the trend currently is to postpone definitive reconstruction after initial decompression of the hydrocolpos when needed.

3.2.2.3 Mayer-Rokitansky-Küster-Hauser syndrome

The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is associated with the congenital absence of a vaginal cavity. Creation of a functional vagina in women with a congenital absence of a vagina can be accomplished using nonsurgical techniques. These should be attempted first, and surgical procedures reserved for those who fail nonsurgical methods.

3.2.2.4 Obstructive müllerian anomalies

Obstructive müllerian anomalies often need to be managed acutely when the adolescent presents with cyclical abdominal pain, pelvic pain, or both, following menarche. Surgical procedures can be associated with complications involving resection of the vagina rather than the septum, which can be difficult to differentiate. Initial surgical management focuses on resection of the septum and reanastomosis of vaginal edges. This can be challenging with thick septa and distortion of the anatomy from hydrometrocolpos. In some instances, a graft may be necessary to bridge the aspects of the intended vaginal edges to be reanastomosed. Complications of excision of transverse vaginal septa include re-obstruction, dyspareunia, and vaginal stenosis, as discussed further in Section 3.2.10.[87,88] Frequently, women present later in life with dyspareunia and constrictive scars requiring surgical management. Revisions are common and tailored to the problem (**Section 3.2.2.5**).

3.2.2.5 Congenital adrenal hyperplasia

Timing of feminizing surgery for girls with CAH remains controversial. Depending on the degree of virilization, surgical management can include clitoroplasty (with or without clitoral reduction) and vaginoplasty. Goals of surgery include construction of gender-compatible genitalia with a view to reproductive and sexual function. Early repair involves clitoroplasty and vaginoplasty in infancy

versus delayed or two-stage repair, which reserves the vaginoplasty until or following puberty. The two-stage approach has the benefit of a drastically reduced revision vaginoplasty compared to the early repair.[89] Reduction of the clitoris, when indicated (severe degrees of virilization), is performed through a neurovascular-sparing technique to preserve sexual function.[90] Reduction of the clitoris by plication of the corpora cavernosa instead of resection is also a possibility.[91]

3.2.3 Surgical options

Surgical creation of a functional vagina is tailored to the GU anomaly. In principle, creation of a functional vagina can be deferred until a woman has completed puberty and committed to maintaining a functional vagina with either dilation or intercourse. Occasionally, as with obstructive müllerian anomalies (complete transverse vaginal septa, leading to obstructed menstruation and pain), there is a need for urgent surgical management, thus extra supportive care must be provided to adolescents and their family. The young women should receive routine follow-up care from initial treatment through the age of sexual maturity in order to assess the functionality.

For women who cannot dilate or do not find the Frank method of dilation acceptable, surgical options exist to create a neovagina. Many procedures for vaginoplasty have been described. This review will focus on the more commonly performed techniques, including surgical traction, creation of a neovaginal space between the bladder and rectum with a graft, and bowel vaginoplasty. The latter procedure is discussed as a matter of historical significance, as it is no longer recommended based on long-term risks.

Several vaginoplasty techniques have been described. Fortunoff and Latimer[92] first described an inverted U-shaped flap technique to open the vagina to the perineum using a skin flap. This technique works best for low-confluence vaginas. A vaginal "pull-through" procedure can be used for high-confluence vaginas, and it was introduced by Hendren and Crawford.[93] In 1997, Peña[94] introduced a new technique derived from cloacal surgeries referred to as total urogenital mobilization, in which the entire urogenital sinus is dissected from the perineum en bloc. Various flaps have been used to augment vaginoplasties.

A recent meta-analysis[95] evaluated sexual function and quality-of-life measures in women with CAH. Four studies including 63 women used the Female Sexual Function Index (FSFI) score to evaluate sexual function. Three of these studies demonstrated differences in sexual function as assessed by FSFI in women with CAH compared to healthy controls. The authors noted that the majority of CAH women were sexually active, but only 48% had "comfortable intercourse" and nearly 20% complained of dyspareunia.

3.2.4 Nonsurgical techniques

The mainstay of nonsurgical vaginal creation hinges around dilatation of the pliable perineal skin; there may be a small dimple to be used as the starting point. Frank first described this method in 1938 using gradually increasing sizes of cylindrical Pyrex tubes.[96] The pressure was self-applied at the introitus. Ingram[97] later modified this procedure by altering the method in which perineal pressure

is applied. Rather than self-applied pressure, he fashioned a dilator built on a bicycle seat. With this strategy, the woman could straddle the bicycle seat and dilator using her own body weight to develop the pressure.

Most modern-day studies employ the Frank method of dilation; it appears to be the most feasible and acceptable to young women. Motivated young women who choose this therapy are typically directed to dilate daily for approximately 6 to 12 months, or until their desired vaginal length is achieved. There is high variability with the length of time required for dilation; this appears to relate to the varying depth of the initial vaginal dimple. Success rates reported in the literature from large case series approach 100%.[98] Reported adverse events are minor and include pain and bleeding.

3.2.5 Surgical traction

In 1965, Vecchietti described a technique in which a traction device is applied to the abdomen with an olive-shaped pellet placed in the vaginal dimple. The two are attached to each other with sutures tunnelled through the peritoneum to the anterior abdominal wall. The sutures are attached to the device and over one week, the mechanical dilation—increased daily—provides a vaginal cavity of adequate width and length. Vecchietti initially described an open procedure, but this has been modified using laparoscopy. Owing to the pain incurred with mechanical dilation, this is usually performed in an inpatient setting.[99,100] This procedure requires pliable perineal tissues, thus cannot be performed in women who have had previous reconstructive procedures or in those with significant scarring.

3.2.6 Creation of a neovaginal space

Another procedure involves the creation of a neovaginal space between the rectum and bladder with placement of a graft. This technique was initially described by Abbe in 1899 and later popularized by McIndoe; it involved placement of a mold with split thickness skin graft from the thigh in the newly dissected neovaginal space (between the rectum and bladder). Many techniques have been described using different types of flaps and skin grafts. The main drawbacks of this procedure include scarring from the skin graft donor site or from the flaps created. Also, women can experience hair growth in the neovagina, depending on the harvest site of the graft or flap. To avoid these complications, other types of tissue have been used as grafts, including amniotic membrane, buccal mucosa, artificial dermis, peritoneum (Davydov), and more recently, acellular matrices.

3.2.7 Davydov procedure

The Davydov procedure[101] uses peritoneum from the pouch of Douglas in a combined abdominoperineal procedure in which the rectovesical space is dissected, the peritoneum is mobilized, and then the peritoneum is attached to the newly created introitus, with the proximal aspect closed using a purse-string suture. Initially described as an open procedure, laparoscopic modifications have afforded women a more acceptable and minimally invasive option.

3.2.8 Bowel vaginoplasty

Bowel segments have been used to create a vagina since the late 1800s. In modern times, sigmoid, cecum, and jejunum are typically the preferred donors. Bleeding, unpleasant discharge, as well as the potential for adenocarcinoma make this procedure less desirable than other methods described above. However, there are a few complex situations where this can still be applied after other options have been tried or discounted.

3.2.9 Functional and sexual outcomes

There are very few data to compare functional and sexual outcomes of different techniques. Many surgeons offer only one technique based on their own training and surgical practice. A recent meta-analysis sought to compare the different surgical techniques. They found that surgical procedures are associated with higher functional success rates as defined as length of the vagina than vaginal dilation (>90% vs 78%), but with more complications. Traction vaginoplasty appears to demonstrate the lowest complication rates combined with highest anatomical success rates, and therefore seems to be the optimal first-line surgical option.[102] Sexual function has been recently assessed with the use of validated sexual questionnaires. Several studies have demonstrated that sexual function is similar in women who underwent surgical or dilator therapy.[103,104]

3.2.10 Revision vaginoplasty

Revision vaginoplasties in women with complex GU anomalies and previous reproductive surgeries are indicated for either dyspareunia, or menstrual or reproductive obstruction. An exam under anesthesia, with or without MRI/vaginogram, vaginoscopy, and cystoscopy is often necessary to plan for surgical revision.

Management of the constricted vagina depends on the location of stricture, depth of vagina, and whether the vagina is connected to a functioning uterus. Most constricted vaginas can be managed with the following procedures: vaginal Z-plasty, grafting, and perineal flaps. When a functional uterus is obstructed secondary to a constricted vagina, the vaginal reconstruction must include anastomosis with the uterus.

3.2.11 Nonsurgical considerations in adolescence and adulthood

3.2.11.1 Physical therapy

Physical therapy is an invaluable aspect of caring for women who have undergone vaginal reconstruction, especially in the case of those with complex GU anomalies. Many women undergoing vaginal reconstruction will develop pain. Sometimes, this is a compensatory "guarding" mechanism of the pelvic floor muscles. Hypertonic pelvic floor muscles contribute to dyspareunia.[105] Appropriate pelvic floor physical therapy aimed at relaxing the pelvic floor musculature can be helpful, both in advance of and following vaginal reconstruction.

3.2.11.2 Psychological support

Women with complex GU anomalies can have poor body image related to the appearance or function of their genitalia.[71,76,81,106,107] Women should be screened for sexual dysfunction with validated questionnaires and referred to qualified women's mental health professionals. This is particularly important and is included in the multidisciplinary approach to women with complex GU anomalies.[98]

3.2.11.3 Preventive gynecologic care

Perhaps the largest misconception among women and their healthcare providers is the inability to have intercourse. Even without a functional vagina, other routes of intercourse, including urethral coitus, have been described in this population causing serious complications.[108] Adolescents and women should be counselled regarding their sexual health and function, with emphasis and focus around safe sex practices and sexually transmitted infection prevention, as well as birth control options.

3.2.12 Fertility challenges in women with complex genitourinary anomalies

3.2.12.1 Congenital adrenal hyperplasia

Women with CAH are known to have decreased fertility, but similar pregnancy rates compared to the general population.[109,110] Early reports[111,112] suggested that spontaneous pregnancy for women with classic CAH without fertility assistance were low (33%–60%). However, more recent reports[109] suggest that spontaneous pregnancy in this group may be much higher, with 91% achieving pregnancy without fertility assistance. In addition, pregnancy rates have been shown to be similar for both salt-wasting and non–salt-wasting subtypes.[109]

Chronic anovulation resulting from excess androgen production is the most common reason for impaired fertility. Glucocorticoid administration is required for ovulation.[113] Ovulation induction and IVF exist as possible options in women who fail to conceive with optimization of their steroid supplementation.[114] Appropriate referral and coordination between endocrine and reproductive specialists is warranted early for women with CAH who are interested in establishing a pregnancy.

3.2.12.2 Exstrophy complex

It is difficult to assess fertility in women with BEEC due to low overall numbers. Deans *et al.*[115] described pregnancy outcomes in women with BE attempting pregnancy. Of the 52 women included in the study, 28 had attempted pregnancy with 19 (68%) reporting success. However, only 4 women were able to conceive spontaneously (21%), demonstrating reduced fertility compared to the general population. Fifteen women underwent evaluation for reduced fertility with the following coexistent diagnoses: endometriosis, tubal obstruction, and polycystic ovarian syndrome. Therefore, women unsuccessfully attempting natural conception in 6 to 12 months should be referred for evaluation by a fertility unit for consideration of assisted reproductive technology (ART). Dy *et al.*[116] reported on 20 pregnancies in 10 women with BE yielding 14 live births. However, the authors did not comment on the methods of conception in these women.

Reports of pregnancy in patients with CE are sparser. A review of the literature[116] demonstrates a study that identified 2 pregnancies in women with CE, one of which was terminated and one of which miscarried. Two full-term pregnancies in women with CE are described by Matthews *et al.*[76] and Gezer *et al.*[117]

3.2.12.3 Müllerian anomalies

Müllerian anomalies are common in the general population, affecting 5% to 9.8% of women[118,119], and very common in women with cloacal anomalies. Depending on the type of müllerian anomaly present, there can be implications for future fertility. A uterine didelphys, or full duplication of the uterus, vagina or both, carries no risk for a woman's fertility, but it does increase preterm birth and malpresentation. This is the most common type of müllerian anomaly seen in women with CE.[120]

A bicornuate uterus results from incomplete fusion of the müllerian ducts at the level of the uterine fundus, yielding 2 separate endometrial cavities. In addition to the increased risk of preterm delivery and malpresentation, approximately 30% to 40% of pregnancies in women with bicornuate uterus end in miscarriage. Despite the adverse reproductive outcomes, no therapy is recommended for women with bicornuate uterus or uterine didelphys.[118] Septa within the uterine cavity have been shown to decrease fertility and increase the risk of miscarriage.[121-123] Resection of a uterine septum has been shown to decrease miscarriage in retrospective studies, with large multicentre trials currently underway.[124] Women with a unicornuate uterus resulting from incomplete development of one müllerian duct are at highest risk for poor pregnancy outcomes, including miscarriage, ectopic pregnancy, and preterm delivery.

In women without a uterus (congenital agenesis or those who have undergone hysterectomy), ART can be used to perform *in vitro* fertilization (IVF) and a surrogate. A recent systematic review reported on 125 women with MRKH syndrome who underwent IVF with gestational carriers yielding 71 live births.[125] Uterine transplantation in women with congenital and acquired absence of uterus is the most recent development with a small series of live births in 7 women.[126] The risks of uterine transplant, specifically for women and offspring with congenitally absent vagina, are not yet defined. When queried about their interest in uterine transplantation, 2 out of 3 of women with MRKH syndrome expressed serious interest.[127]

3.2.13 Labour and delivery considerations in women with complex genitourinary anomalies

The goals of labour and delivery in women with complex GU anomalies are the same as within the general population: to provide a safe experience for both the baby and the mother. In the case of a previously reconstructed GU tract, the mother can face significant morbidity if the appropriate precautions are not taken.[115] As mentioned above, women with prior bladder neck operations, unfavourable pelvic morphology, gestational comorbidities, or fetal malpresentation (all of which are more common in women with congenital GU conditions), planned cesarean section is often favoured. Maternal risk associated with cesarean section is increased in women with multiple abdominopelvic surgeries. Ureteral transection and fistula formation was reported in Deans'[115] series of 31 women with live births. Matthews *et al.*[76] also reported a significant surgical morbidity in a woman with CE

who had perforation of her Kock pouch at the time of cesarean section, resulting in fistula formation. Attempts to avoid emergency cesarean delivery should be made, as risks for surgical morbidity are high in these circumstances.[78]

3.2.13.1 Menopause

There are no studies about the effects of menopause in women with SB, probably because historically, few women in this patient group reached this age. Premature menopause and all the ramifications of hormonal changes are most likely exacerbated in women with SB due to lack of mobility, and associated bladder and bowel dysfunction.[128] Osteoporosis risk, already high in this population, is even higher after menopause.

3.2.13.1.1 Recommendation

- During menopause, appropriate screening and treatment by a bone health specialist should be considered.

3.2.14 Pelvic organ prolapse in bladder exstrophy and spina bifida

Pelvic organ prolapse (POP) refers to the descent of female pelvic structures (bladder, uterus, cervix, vault of vagina posthysterectomy, small or large bowel, rectum) into the vagina, due to loss or weakening of the support mechanisms of these structures. POP is very common, with a prevalence of 45% in the general female population.[129] In the general adult female population, prolapse has been found to occur most frequently in the anterior compartment, followed by in the posterior compartment, with occurrence of prolapse in the apical compartment the least common.[130] Several studies throughout the literature have found aging, childbirth, prior pelvic surgery (including hysterectomy), and other causes of compromised pelvic floor muscle strength, as well as voiding and defecatory disorders, to be associated with the development of POP. Asymptomatic POP is very common in the general population and it is mainly associated with stage 1 or 2.

Women with congenital spinal dysraphism (e.g., SB) and sacral agenesis, as well as women born with BE and CE, present a unique patient population when it comes to pelvic structures and their support. With advances in the treatment and management of these patients, these women are living longer into adulthood and experiencing adult problems such as POP, which may cause exacerbation of other adult issues such as sexual dysfunction, difficulties with achieving pregnancy, and challenges with clean intermittent catheterization (CIC). A limited number of studies have evaluated POP in women with congenital urological abnormalities. Despite the paucity of data, women in this patient population often present with POP at a much younger age, at higher stage of prolapse, and are far more likely to be nulliparous at presentation. Given these factors, screening and managing POP in women with a history of congenital spinal dysraphism or BE presents a unique challenge, as concerns regarding management of POP in women, often before childbearing, must be taken into consideration.

3.2.14.1 Epidemiology

One series[137] identified a total of 33 female patients with SB who demonstrated POP at a mean age of 33.2 years. The incidence of POP in the studied population was staggering, with 85% (28/33 patients) having some degree of prolapse and 48% (16/33 patients) demonstrating stage 2 prolapse or greater. Additionally, 24 patients in this cohort (72.7%) were nulliparous, and 12 of the 24 nulliparous patients (50%) demonstrated prolapse.

Another retrospective review of adults with congenital GU abnormalities reported 7 out of 40 patients with clinically bothersome POP at a mean age of 22.8 years. Of the patients with POP, there were 4 patients with myelomeningocele, 1 patient with sacral agenesis, and 1 patient with BE. The majority (71%) were nulliparous. The mean stage of anterior compartment prolapse on the Pelvic Organ Prolapse quantification (POP-Q) was stage 3. It is important to note that women with SB and BE present at a younger age compared to unaffected women, where the average age of presentation has been estimated at 44 years.[138]

POP presents special challenges in the BEEC population. O'Kelly *et al.*[131] found the incidence of POP to be as high as 50% in patients with BE who had undergone complete primary repair of BE. Like findings in the population of females with SB, this study found that adult women with a history of BE present with POP at a much younger age, higher stage, and with or without prior sexual activity or pregnancy.

Although patients with myelomeningocele and BE both present with POP upon reaching young adulthood, the patients in each group have distinct anatomical differences, risk factors, and etiologies of developing POP.

3.2.14.2 Bladder exstrophy-epispadias complex

The literature[76] reports that POP occurs in 20% to 30% of women born with BE, although the true incidence is likely much higher with aging. There are several different anatomical risk factors that place this patient group in a higher risk category of developing POP. Female patients with BE have pubic diastasis, altered pelvic floor musculature, and anterior displacement of vagina, anus, labia majora, and clitoris. As pubic diastasis tends to widen with overall growth of the patient, the labia and clitoris often are pulled in divergent directions. Kaufman *et al.*[132] explained that due to the primary goal of pelvic osteotomy to reduce pubic diastasis and realign the pelvic floor musculature, it has been postulated in the literature that pelvic osteotomy decreases the risk of developing POP. Indeed, there is evidence[133] that pelvic osteotomy does lead to improved continence after staged bladder neck reconstruction in patients with BE.

However, further studies show no correlation between pelvic osteotomy and the risk of developing future prolapse. Instead, there is a significant relationship between the degree of pubic diastasis as an adult and the risk of developing prolapse. Significant deficiencies in the functioning of the pelvic floor support system, most notably of the levator ani musculature, are implicated in impaired anterior support.[134] In addition, the ligaments supporting the uterus, (cardinal ligaments) are weaker in women with BEEC, further impairing uterine and apical support.

Given the significant anatomical abnormalities in patients with BE, one would think that subsequent surgical repair of these patients or staged repair would result in improvement of the risk factors contributing to POP. However, surgical repair of BE is itself a risk factor for the development of POP.[135]

3.2.14.3 Myelomeningocele

Women with SB also are at increased risk of developing POP due to a variety of risk factors, including intrinsic anatomical risk factors as well as body habitus and stool habits. Due to the neurological deficit, women with SB often demonstrate pelvic floor muscle atrophy. Prior pelvic surgeries may further increase the risk for prolapse. A major general risk factor in developing POP is obesity, which is estimated to impact over one-third adults with SB.[136]

Extrinsic pelvic stressors are also inherent to living with SB. Neurogenic bowel dysfunction typically results in chronic constipation and resultant straining with bowel movements. For some patients, Valsalva voiding may further impact the pelvic floor. As many of these patients have limitations on their mobility and thus must use assistive devices such as wheelchairs, they often need to transfer from bed and transportation vehicles to assistive devices several times during the day. Transferring also puts a significant stress on the pelvic floor supporting musculature.

3.2.14.4 Clinical evaluation

3.2.14.4.1 History

When taking a history, the healthcare provider should specifically ask female patients with BEEC or SB about symptoms of prolapse, including feeling or seeing a bulge in the perineal area, or trouble performing self-catheterization due to a bulge. The provider should also evaluate what effect, if any, the prolapse is having on the patient's overall quality of life by asking about dyspareunia and challenges around bowel and bladder management. As with any patient presenting with prolapse, the provider should ask about the need to reduce the prolapse manually (splinting) to aid in bowel or bladder evacuation. Additionally, a discussion of continence status is essential. The provider should ask the patient if urinary incontinence exists, and if so, the nature of incontinence (if it related to a sensation of urinary urgency and frequency, if it occurs only with stress manoeuvres, or a combination of these symptoms). If the patient performs self-catheterization for bladder management through the native urethra, the provider should ask the patient about recent difficulty catheterizing or urinary incontinence between catheterizations.

Given the sensory neurological deficit experienced by patients with SB, affected women may not report the sensation of a vaginal bulge. In one study[137], only one-third of these patients who had advanced-stage prolapse reported prolapse symptoms, 2 of whom reported dyspareunia. All patients who reported symptoms of prolapse stated that they noted a bulge during routine care, typically during self-catheterization.

Diagnosis may prove more challenging by symptoms alone when the patient performs CIC via a catheterizable channel, as demonstrated in one study.[138] A thorough gynecological and obstetric history, including gravity, parity, type of delivery (vaginal or cesarean section), hormonal status (pre- or postmenopausal), and use of exogenous hormones (oral contraceptive pills, topical or systemic estrogen), is likewise essential. As discussed above, women with BEEC and SB are more likely to be

nulliparous at presentation of POP. Management of POP in nulliparous patients needs to be tailored to the patients' desire for future pregnancy. For women who express a desire for pregnancy, surgical treatment may best be deferred until after completion of pregnancies if possible.

A detailed surgical history is important in planning future treatment, including additional surgery. This should include prior history of hysterectomy, prior anti-incontinence surgery (urethral bulking agent, sling, bladder neck closure), and prior prolapse repairs. If future pelvic surgeries are under consideration, prolapse surgery may be performed concomitant with the other procedures, thereby minimizing overall morbidity for the patient.

3.2.14.4.2 Physical examination

Prior to performing abdominal and pelvic examinations, the provider can often obtain significant information from the general appearance of a patient, including factors such as age, gait, necessity for devices to assist mobility (wheelchair, braces, canes), stature, and frailty.[139] Abdominal examination with a focus on prior surgical scars, presence of hernias, bladder distention, and body habitus is especially important for surgical planning purposes. The female pelvic examination will provide the bulk of diagnostic information when it comes to POP evaluation. Some young women never have had a prior pelvic examination, and this may prove physically and emotionally traumatic to young patients. For patients who experience severe distress over genital and pelvic exams, consideration should be given to sedation or examination under anesthesia to minimize patient distress.

The provider should evaluate the external genitalia in terms of general appearance, hair distribution, presence of any lesions, scars suggestive of prior anti-incontinence procedures, as well as size of labia and estrogenization of tissues. The urethral meatus can be assessed for correct size, location, and presence of urethral prolapse, and the urethra can be palpated for presence of any lesions, mesh or sling material, as well as urethral diverticula. Urethral position and mobility should be assessed at rest, and with cough and Valsalva manoeuvres.

During physical examination, the anterior wall can be supported, and an evaluation of stress incontinence should be performed with the prolapse reduced. In general, prolapse assessment is recommended to be performed in both the lithotomy and standing position, with evaluation of the anterior, posterior, and apical compartments while the patient is at rest, coughing, and straining. However, this is often not feasible in nonambulatory patients with SB. A surrogate examination by asking the patient to sit upright and mimic a transfer on the examination table may prove diagnostic.

While the general adult female population is most at risk for anterior compartment prolapse, studies suggest that patients with SB are at greatest risk of apical descent. Indeed, the patients with stage 3 and 4 prolapse presented almost exclusively with apical compartment descent. Unlike in the general population, in which severity of anterior prolapse correlates with apical descent, this correlation does not hold in patients with SB.

3.2.14.4.3 Diagnostic testing

In the general adult female population, there is a lack of consensus on the diagnostic testing recommended in the treatment of POP beyond postvoid residual urine volume and urinalysis. Advanced testing is often warranted for women with SB and BEEC, given the complex nature of their presentation and histories. Such testing may include video urodynamics, pelvic magnetic resonance imaging, cystoscopy, and other procedures as preferred by the treating providers.

The authors recommend video urodynamics for evaluation of neurogenic bladder in this group, particularly to assess the bladder or outlet, which may require attention concurrent with the prolapse.

3.2.15 Management

Prolapse management must also be tailored to each individual patient's anatomy, medical comorbidities, bowel and bladder function, and family planning goals.

3.2.15.1 Nonsurgical management

Nonsurgical management of POP includes observation, pelvic-floor muscle training (PFMT), and pessaries. In the general adult female population, PFMT has been shown to demonstrate improvement in POP-related quality of life, improved activity, and improved sexual function.[139] However, PFMT is a nonsurgical treatment modality associated with high cost as well as poor long-term efficacy.[140] PFMT may prove additionally challenging in women with BEEC and SB. First, the more advanced stage of prolapse in this population is less amenable to correction with PFMT. Second, PFMT requires sensory and motor integration that is often lacking in the pelvic muscles of patients with SB. There is no literature to support use of PFMT in prevention or treatment of POP in these patient populations.

Pessaries are a well-described treatment for prolapse in the general population, particularly those who are unwilling or unable to undergo surgery. Pessaries must be initially fitted by a medical professional, and routine follow-up and maintenance with a medical professional is required. In the SB population, a pessary may be a particularly effective treatment option in carefully selected nulliparous women desiring future fertility. The group studied by Khavari *et al.*[138] had one nulliparous patient who desired further fertility. One concern raised about use of pessaries in women who are insensate relates to vaginal or rectal erosion risk.[141] Patients with BEEC, however, have a short and anteriorly displaced vagina that often cannot accommodate or hold a pessary in place. Pessaries have been demonstrated to have limited durability in women with BEEC for this reason.[142]

3.2.15.2 Surgical management and outcomes of surgical correction

As with nonsurgical prolapse management, surgical management of prolapse must involve a shared decision-making process between the patient, her family, and the healthcare provider. Prolapse treatment must consider the patient's personal situation, including desire for future fertility, medical needs including bladder and bowel management and incontinence, and individual anatomical factors. In both the SB and BE populations, several different surgical management techniques have been described, yet little data exist to support one technique over another.

Outcomes for patients undergoing surgical POP correction are limited to small series with short follow-up. One series[138] that included 5 patients undergoing laparoscopic sacrocolpopexy (1) and transvaginal hysterectomy with uterosacral ligament suspension (4) demonstrated a 20% failure rate at a mean follow-up of 17.6 months. Another series that included patients with BEEC specifically demonstrated a >50% chance of failure after first transvaginal repair. However, greater success was demonstrated with abdominal sacrocolpopexy with biological or synthetic grafts, albeit with a 33% failure rate.[143] Along with abdominal sacrocolpopexy, several other surgical treatment options for POP in patients with BEEC have been presented in the literature, including abdominal and vaginal hysterectomy, abdominal and vaginal synthetic grafts, uterine fixation to the anterior abdominal wall, round ligament suspension, and robotic-assisted sacrouteropexy.[144] The common challenge that runs through surgical management of POP in patients with BE is that there are limited options for vaginal approaches to POP repair due to the particular anatomy of these patients, specifically, the short vaginal vault and lack of vaginal angulation. In addition, patients with BEEC have significant deficiencies in the pelvic support structures, such as the sarcospinous ligament, which are the mainstay of support when it comes to vaginal repair of prolapse, thus making vaginal repair of prolapse in this population quite difficult.

In considering future fertility goals, the surgeon must keep in mind the risk of recurrence of POP after pregnancy in a woman who has had prolapse repair prior to childbearing. Previously repaired prolapse in patients with BE has been shown to have a high likelihood of recurrence after parturition.[145]

3.2.15.2.1 Conclusion

- Women with SB and BEEC experience POP at a younger age, more advanced stage, and with nulliparity, and the manifestations of POP can be atypical, given anatomic and neurological comorbidities in these women. Advanced POP can impair bladder emptying and lead to bowel complications, vaginal ulceration, and hydronephrosis with upper tract deterioration. Therefore, female patients should be screened with a history focusing on vaginal bulge, dyspareunia, and trouble performing CIC, and pelvic exam beginning in their third decade of life. The decision on how to manage POP once it is diagnosed is a complex one, incorporating the patient's desire for treatment, interest in future fertility, and current medical conditions, including bowel and bladder management and incontinence. Surgery should be offered only by surgeons experienced in POP repair and, if possible, delayed until after child-bearing.

3.2.16 Male genitoplasty for bladder exstrophy-epispadias complex

A short phallus in BEEC is related to intrinsic corporal deficiency as well as pubic diastasis. Dorsal chordee may be due to corporal disproportion, with or without a short urethral plate (UP). Furthermore, in some cases, repeat surgery causes iatrogenic scarring contributing to chordee (**Figure 3-2**). Recently, this author's experience[146] was reviewed in 33 patients who underwent secondary repair of the genitalia aiming at penile lengthening and correction of dorsal penile chordee. There were 30 adolescent or adult patients born with BE and 3 patients born with incontinent epispadias. Their ages ranged between 12 and 29 years. While some of the patients had undergone urinary diversion, in all cases, the urethra served as a conduit for seminal fluid. Penile lengthening (Johnston procedure) was performed in all patients. The corporal body was dissected and detached from the inferior pubic ramus. The mobilization stopped short of the ischial tuberosity to avoid injury to the pudendal nerves and vessels as they emerge from the Alcock canal. In 9 patients with extensive scarring, the periosteum was incised, and subperiosteal dissection was performed to preserve the

corporal wall and erectile tissue. The urethra was also dissected and placed in the groove between the corpora prior to suturing the corpora together. In 13 patients, the urethra was augmented as well. The dorsal penile curvature due to corporal disproportion was corrected using dermal grafts in half of the patients (**Table 3-1** and **Table 3-2**). Follow-up ranged from 2 to 12 years. Complications included subcutaneous hematoma (which required drainage), wound infection with distal dehiscence of the repair, recurrent scarring and keloid formation, and urethral stricture. All patients gained various degrees of penile lengthening and most were satisfied with the surgical outcome.

Correcting the diastasis of the pubic bones does not always increase the functional length of the penis. This is because correction of the skeletal anomaly leads to tilting of the pelvis, resulting in more horizontal lie of the pubo-ischial rami where the penis retracts and becomes less prominent than before. Furthermore, performing osteotomies in adult men with BEEC to increase penile length has proven ineffective and often hazardous. In an exstrophy-epispadias penis, the position of the neurovascular bundles is found to be more caudally displaced rather than the normal dorsal location of the neurovascular bundles on the penile shaft. The bundles become more proximal and approach the point at which the corpora join the pubic bones; as they join the pubic bones, they course more anteriorly and bundles become difficult to trace, merging into the cleft between the corpora and the pubic bones. To minimize the devascularization risk, Johnston[147] proposed partial rather than complete mobilization of the corpora, as originally described by Kelly and Eraklis.[148] A subperiosteal approach in revision surgeries provides "a virgin" surgical field, and it protects the neurovascular and erectile structures.

If the neourethra is deficient, dorsal chordee may be exacerbated in some instances. In other cases, dorsal-ventral corporal disproportion or scarring may predominate, contributing to the dorsal chordee. A close inspection of the penis, urethra on stretch, and with artificial erection can help distinguish which of these entities is most contributory prior to making treatment decisions.

FIGURE 3–2
A) Scarred abdominal wall, epispadias and dorsal chordee due to scarring; **B**) excision of scarred tissues and tubed urethroplasty (arrow); **C**) advancement flap for resurfacing the abdominal wall and rotation flap for the penis; **D**) six months postsurgery.

Images courtesy of Dr. Moneer Hanna.

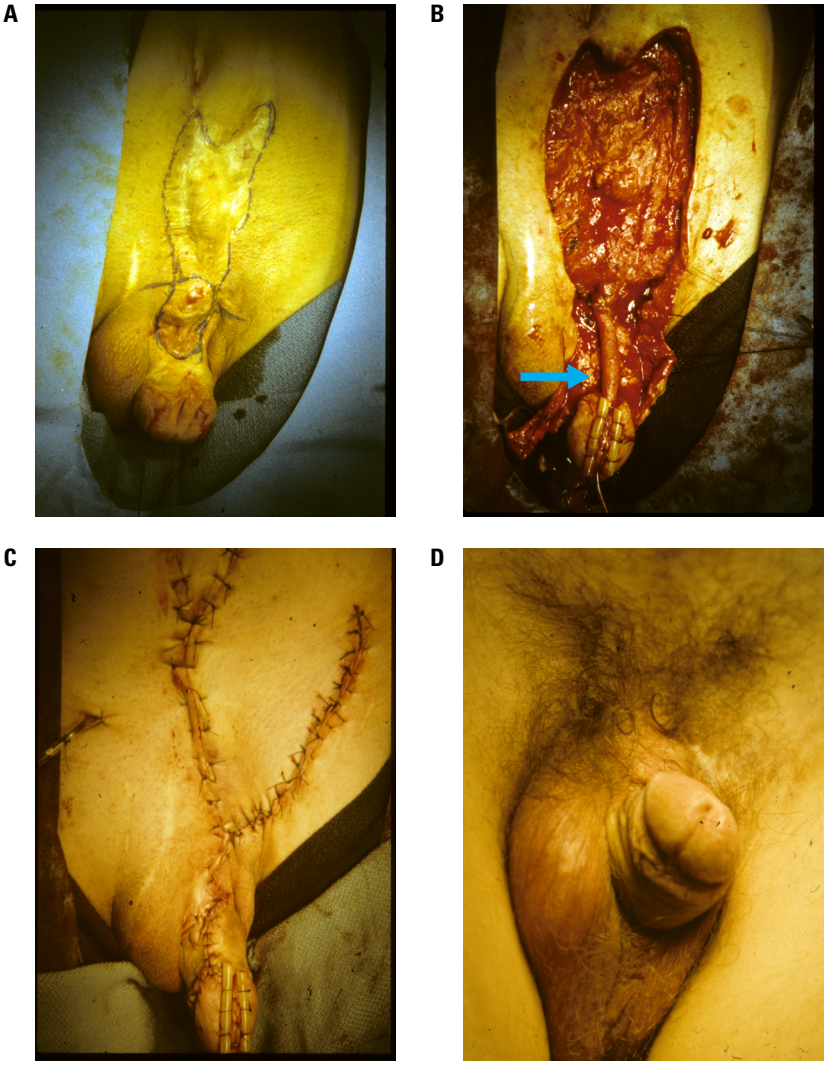


TABLE 3–1 Chordee Repair of 33 Patients

Procedure	Number of patients
Release of scarring, with or without AlloDerm filler	17
Dermal graft dorsal corporoplasty	16

AlloDerm® (LifeCell Corp.; Brancburg, NJ).

Adapted from: Bonitz RP, Hanna MK. Use of human acellular dermal matrix during classic bladder exstrophy repair. *J Pediatr Urol.* 2016;12:114.e1–114.e5.

TABLE 3–2 Penile Lengthening (Urethra)

	Number of patients
Terminal meatus	13
Tubed full-thickness skin graft	4
Tubed buccal mucosa	9
Hypospadias/epispadias meatus	20

Adapted from: Bonitz RP, Hanna MK. Use of human acellular dermal matrix during classic bladder exstrophy repair. *J Pediatr Urol.* 2016;12:114.e1–114.e5

3.3 Hypospadias

Hypospadias is the most common congenital anomaly of the penis, occurring in approximately 1 in 292 live births.[149] It refers to incomplete urethral development that results in a meatus that can be located anywhere from the perineum to the proximal glans. Additionally, the penis may curve downward and may have a dorsal hooded foreskin that is deficient ventrally. The variable combinations of these abnormalities make management of hypospadias a complex issue.[150]

The aim of hypospadias repair is to correct the appearance of the penis, allow voiding while standing, and improve fertility by enabling distal penile ejaculation and correcting the penile curvature.[151-153]

Studies with a large sample size and long-term follow-up quote 10% to 60% reoperation rates, depending on hypospadias severity. Boys with more proximal hypospadias carry a greater risk for complications. One study[154] with 3,186 hypospadias surgeries in Australia from 2001 to 2010 reported on a 13% overall complication rate, with a 33% rate for proximal hypospadias cases; 52% of the complications occurred more than a year postsurgery and some up to 5 years later. Snodgrass[155] followed up on 1,140 cases and found that the chance for repeat complications was even higher than for the initial operation. As expected, the more severe and proximal the hypospadias, the more common a subsequent procedure was required.[156] A single procedure "corrected" distal hypospadias in 79% of cases versus 48% of cases of proximal hypospadias. In other words, 1 out 5 boys with distal hypospadias underwent more than 1 operation because of complications.

3.3.1 Management of reconstruction complications

Failed hypospadias complex includes cases of several unsuccessful attempts at hypospadias repair. These may present clinically as recurrent strictures, urethrocutaneous fistulas, glans dehiscence, urethral dehiscence, chordee, or glans deformity. In the literature[157], various surgeries and techniques have been described for revision hypospadias repair. However, there is no uniformity in the guidelines for management of failed hypospadias. The term "failed hypospadias," or cripple, was coined for individuals with residual functional abnormalities after multiple failed attempts at hypospadias repair. These include recurrent strictures, urethrocutaneous fistulas, glans dehiscence, urethral dehiscence, chordee, and glans deformity. Repeated surgery increases the risk of fistula and stricture formation due to the deficiency in ventral dartos and poor blood supply. The majority of hypospadias cripples have had more than 3 prior unsuccessful attempts at urethroplasty.[158]

3.3.1.1 History and examination

A detailed history of all patients should include the type of prior repair attempted. Evaluation should include:

- The length of the penis
- Availability of penile skin for reconstruction
- Shape of the glans (size and depth of glans cleft)
- The width of UP
- The presence of urethrocutaneous fistulae
- Scrotal morphology, including webbing and transposition
- Coexisting chordee
- Scars

A uroflowmetry may be helpful to determine voiding pattern and investigate for presence of urethrocutaneous fistulae. A retrograde urethrogram or cystoscopy may likewise help determine urethral stenosis and coexisting fistulae. Many algorithms have been developed to deal with cripple hypospadias; however, there is no established consensus.

3.3.1.2 Surgical techniques: urethroplasty

The quality of existing neo-UP often drives surgical decision-making: if it is heavily scarred, metaplastic, or contains hair and stones, partial or total resection may be prudent, necessitating a staged reconstruction.[159] Furthermore, the possibility of a single-stage repair versus a two-stage surgery often depends on the width of the UP, the size of the glans, and degree of coexisting chordee. It is suggested that a plate larger than 8 mm can be augmented with buccal graft as dorsal inlay and tubularized at the same time (**Figure 3-3**). Most hypospadias cripples require a 2-stage approach. Traditionally, a 2-staged urethroplasty involves application of oral mucosa in the first stage as a plate, followed by subsequent tubularization, usually after 6 months (**Figure 3-4**).

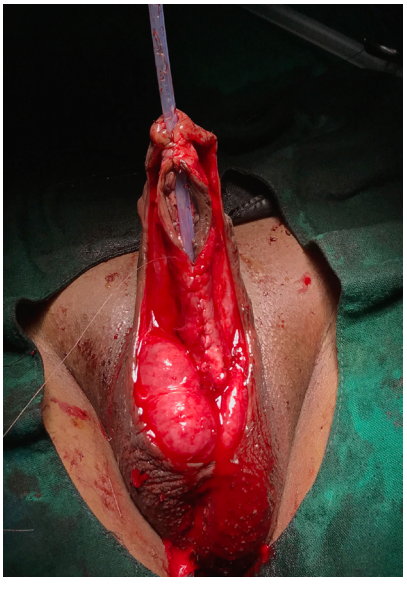
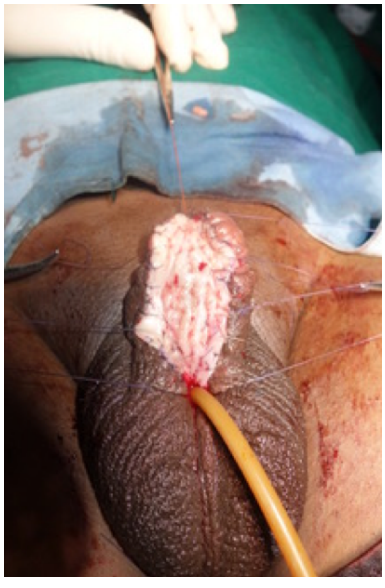


FIGURE 3–3
Penile urethral stricture post hypospadias surgery. Urethral plate was larger then 8 mm. Dorsal inlay buccal mucosa graft with tubularization at the same time.

Images courtesy of Dr. Kularni S and Pankaj.

FIGURE 3–4
First stage of a two-stage repair. Old urethral plate is resected and a first stage is performed with a quilted buccal mucosa graft. Six months later, the second stage operation is performed.

Images courtesy of Dr. Kularni S and Pankaj.



Various graft tissues are used, buccal or lingual mucosa being part of the armamentarium.[159-161] There is a tendency for pediatric surgeons to use lip graft. Adult hypospadiologists and reconstructive urologists more commonly use cheek or tongue grafts.[162,163] Rectal mucosa has recently been described in some instances where availability of oral mucosa is insufficient for repair.[164]

Adult reconstructive experts do not believe in excising any existent plate unless it is extremely scarred. Each and every millimeter of native urethra is helpful for reconstructing a wide urethra. A buccal graft can be split and inserted around the UP if necessary rather than excision of the plate.[165]

In the second stage, peri-urethral lateral incisions are made and the neourethra is constructed. There should be minimal mobilization of the edges of the graft. In case there is scarring of the UP, an additional small graft can be inserted as dorsal inlay augmentation. Dartos can be used to cover the urethral repair if there is some; if not, tunica vaginalis, orphan spermatic cord, or other local tissues can be applied. In various high-volume units, the graft contraction after a staged buccal graft is as high as 39%.[166]

Alternative staged approaches are used in different geographies, including simply opening the urethra at the first stage (Johanson procedure) and applying a dorsal inlay graft at the second stage (Asopa procedure).[167] A review of all techniques in detail is beyond the scope of this manuscript and no single approach has been proven superior to another.

Hypospadias repairs may use the available local skin to form the wall of the urethra. In some cases, this is a hair-bearing skin, which results in formation of hairballs in the urethra over a period of time. There may be stone formation. Patients have presented with hair coming out of urethra, urethralgia or dysuria, feeling a stone in their urethra on palpation, or recurrent UTI. This is a challenging situation. If the penile urethra has a stricture, it can be incised ventrally, the hair removed, the skin reduced, the dorsal buccal graft inserted, and the urethra tubularized. Complete excision and replacement

by buccal graft in a staged approach may sometimes be necessary. Endoscopic interventions may be reasonable in situations where the urethra is not stenosed and the hair burden reasonable, including CO_2 laser desiccation, yttrium aluminum garnet (YAG) laser photocoagulation, grasper extraction, diode laser, electrolysis, and hair tricholysis with thioglycolate or open surgery revision.

3.3.1.3 Surgical techniques: fistula repair

Fistulae may form either as a result of distal stricture, or spontaneously, in the absence of distal stricture. The management depends on the size of meatus and concomitant presence of urethral stricture. If the urethra and meatus are of a normal calibre, then urethrocutaneous fistula can be closed primarily. Simple fistula repair, either with coring out of the fistula from the outside in or inversion of the fistula into the urethra with secondary amputation, can be performed.

3.3.1.4 Surgical techniques: sacculation

A normal urethra has good support from the corpus spongiosum. After hypospadias repair, the spongiosum may be deficient. Prior use of unsupported skin grafts or pedicled flaps lead to diverticulum formation over time. Revision includes reduction or retubularization, or replacement urethroplasty with plication with dartos, if the corpus spongiosum is deficient.

3.3.2 Chordee and curvature

Penile curvature is a common feature associated with hypospadias and presents with variable levels of severity among these patients. Chordee repair can be straightforward in cases of mild curvature, but its correction can be challenging, depending on the severity and penile length. Mild penile curvatures can be corrected by simple techniques like penile degloving and dorsal plication, while severe forms often require more complex techniques.

Ventral curvature (VC) of the penis is normally seen until the 25th week of gestation.[168] Disturbance in urethral embryonic development may result in hypospadias with curvature. Moreover, abnormality across the ventral penile axis is noticed in these patients alongside with hypodevelopment of the spongiosum that ultimately leads to ventral penile disproportion and curvature. Several theories[169-171] to explain the etiology of ventral penile curvatures exist: abnormal development of the UP; fibrotic mesenchymal tissue at the urethral meatus; and ventrodorsal corporal disproportion. Moreover, as recently highlighted through elastosonographic evaluation of hypospadiac patients, the spongiosum can be stiffer and less elastic, and the cavernous corpora less developed.[172] Recurrence of chordee occurs due to one of several factors: inadequate evaluation of chordee at the initial surgery, leaving uncorrected curvature; inappropriate technical choices for chordee correction; disproportionate growth of the UP and ventral corpora cavernosa and fibrosis of previous urethroplasties and corporoplasties.

Although congenital chordee occurs in about one-fourth of all hypospadias patients[173], it is found more frequently in severe types, approximately 11% in patients with distal hypospadias[174] and 81% in patients with proximal hypospadias.[175] While congenital chordee can occur in lateral dorsal or ventral directions, chordee associated with hypospadias is always ventral. There is considerable controversy over how to evaluate the degree of ventral penile curvature, and most series present data based on the severity measured empirically and classified as mild (<30°), moderate (30°–50°), or severe (>50°).[27,176]

Ideally, the severity of chordee should be measured objectively using a goniometer or measuring the angles with digital photography. Historically, persistent or recurrent VC after hypospadias repair may occur in approximately in 20% to 30% of patients.[177] Unfortunately, there is still recurrence of VC, despite testing it during the initial repair using artificial erection techniques. Late presentation of chordee recurrence is common, due to patient fear of surgery, ignorance, or embarrassment.[178]

Fraumann *et al.*[179] evaluated the long-term outcomes on adults who underwent severe hypospadias repair during childhood. Of the 13 patients with long-term follow-up, 4 (31.0%) patients reported curvature <30° and 1 reported curvature >30°. Interestingly, despite having persistent VC, only 2 patients described the overall penile appearance as "somewhat unsatisfactory" or "very unsatisfactory." Bubanj *et al.*[180] followed hypospadias patients after puberty and found that a high number had VC during erection when compared to controls (40% vs. 18%), emphasizing the importance of long-term follow-up in this population. Among patients undergoing tubularized incised plate (TIP) and VC repair in infancy, almost half (43%) were shown to have successful correction with skin release alone.[181] Recurrence of curvature is an under-reported problem due to the difficulty establishing long-term follow-up with adolescents, who, even if not satisfied, rarely participate in surveys or long-term studies.[182] As we can see, these studies support the paramount importance of long-term follow-up for this population.[183,184]

When patients with recurrence of VC seek medical attention, they often have other associated urethral abnormalities, namely, strictures, recurrent UTIs, orchiepididymitis, and weak urinary stream.[185]

3.3.2.1 Indications for intervention with recurrent chordee

Painful erections, penile pain with intercourse, or inability to penetrate are the usual symptoms that prompt patients to seek treatment.[178] The induction of artificial erection during hypospadias repair was a significant advancement at the initial repair, but unfortunately, it does not prevent later recurrence of VC, especially in cases where the UP was incorporated in the repair (such as in onlay island flap urethroplasties).[186,187] Such recurrences may not be diagnosed initially after surgery, but only later on at puberty, when the patient himself pays more attention to the shape of his penis, once more underscoring the importance of long-term follow-up until puberty for this population.[181] Vandersteen *et al.*[178] reported their long-term follow-up of 22 adults operated for proximal hypospadias in childhood. Interestingly, these patients started noticing the recurrence of VC 12 to 18 years after the initial surgery. Fourteen of the 22 patients attempted sexual intercourse, 8 had severe pain, and 6 were unable to have vaginal penetration due to significant curvature. Repeated corporoplasty was required in 15 patients (68%).

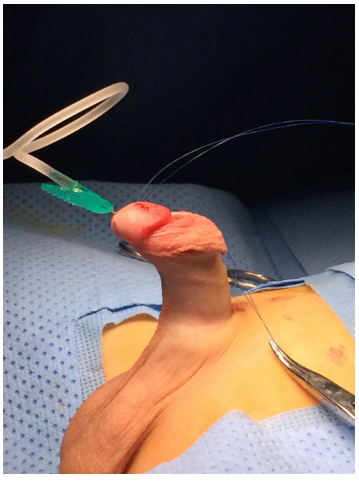
3.3.2.2 Surgical correction

The initial step for correction of persistent chordee consists in urethroscopy or urethrogram in order to rule out associated urethral abnormalities. If the urethra is endoscopically normal, the next step is to perform penile degloving to release skin and ventral fibrotic tissue. Artificial erection before and after degloving is necessary to demonstrate degree and morphology of angulation (**Figure 3-5**). The resolution rate of the penile curvature after the dissection of the skin and the dartos fascia in patients with primary hypospadias was found to be 70% in the mild form (<30°), 30% in the moderate form (30°–45°), and 2.4% in severe curvature (>45°).[188]

FIGURE 3–5
A fine butterfly needle is entered in one of the corporal bodies, preferably through the glans. Perineal pressure is given and saline is injected until an erection is obtained. This figure shows a mild ventral curvature.

In older boys with a distal curvature, a tourniquet around the base of the penis can be helpful.

Images courtesy of Dr. Joao Pippi Salle.



3.3.2.3 Plication

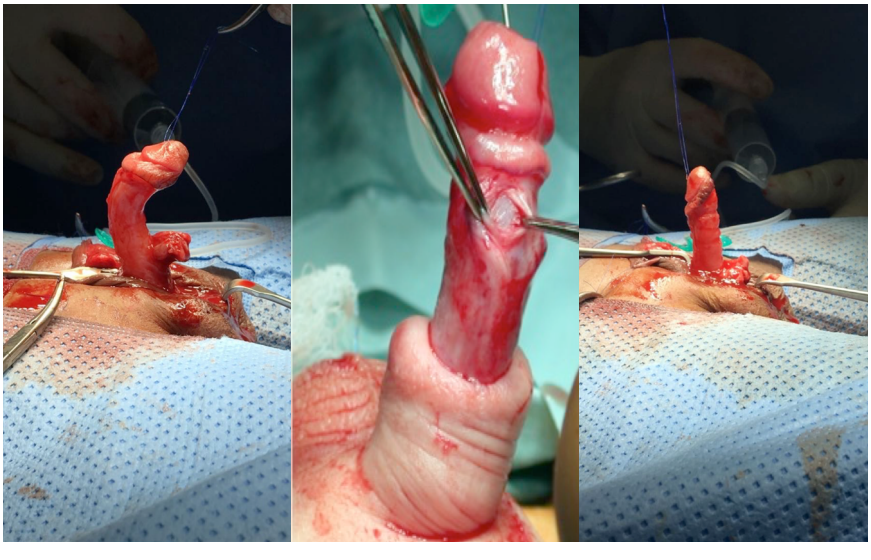
Mild degrees of VC can be corrected with dorsal plication (**Figure 3-6**). The plication principle was first published by Nesbit in 1965,[239] and modified by Baskin and Duckett[189], followed by several other descriptions.[190] Since then, midline dorsal plication of the tunica albuginea has become the procedure of choice in most patients with persistent mild curvature (<30°) following degloving. Although Baskin proposed the simple midline plication without exposing the albuginea, some prefer to incise the Bucks fascia, laterally retract the neurovascular structures often present, expose and incise the albuginea, and plicate it using non- or slowly absorbable sutures. In so doing, one does not rely on the strength of the stitch alone, but also on the associated scarring that is created by the incision. Recurrence of VC after plication on the dorsal surface was reported in 7% of patients.[191] Moreover, Chertin *et al.*[192] reported a recurrence of chordee in 6 of 28 patients (21.4%) who initially underwent dorsal plication surgery for chordee (>30°). Consequently, other techniques must be considered if a curvature >30° to 40° persists after degloving and dissection down to the base of the penis.

FIGURE 3–6
A Artificial erection is performed

B A dorsal midline incision is made at the level of the dorsal vein. The plain fond at the midline doesn't contain many nerves. Dissection is made until the level of the tunica albuginea of the corporal bodies. There, a midline plication is performed.

C Artificial erection after a dorsal midline plication. A straight penis is observed.

Images courtesy of Dr. Joao Pippi Salle.

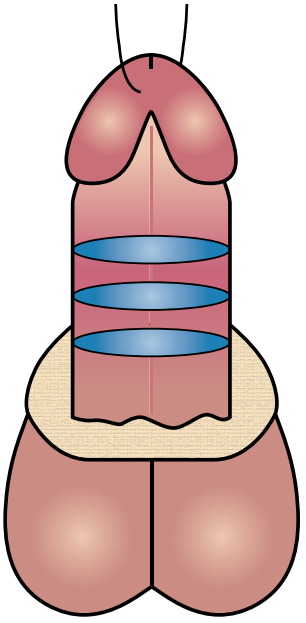


3.3.2.4 Urethral mobilization

A stepwise approach using extensive urethral mobilization all the way to the bulbar urethra has been proposed by some authors[175,176,193] to correct penile curvature. Snodgrass and Prieto[175] reported that straightening of the penis with UP preservation could be achieved in 85% of cases when all these manoeuvres are performed. The same authors later reported a very high rate of secondary urethral strictures after extensive mobilization, and they therefore recommended discontinuation of this approach. Pippi Salle *et al.*[194] have confirmed these findings and reported a high VC recurrence rate after TIP repair and UP mobilization. Therefore, they advised caution when a long TIP repair is performed, suggesting its use only in cases of mild or no chordee with favourable UP (i.e., pliable, good spongiosum, and deep groove). Other manoeuvres, such as external corporeal rotation, multiple deep transverse corporotomies or corporotomy, and grafting, are also used as alternatives for chordee correction (**Figure 3-7**).[195,196]

FIGURE 3–7
After resection of the urethral plate, three ventral transversal incisions in the tunica of the corporal bodies are made in order to obtain a straight penis. This technique is only applied in severe curvatures.

Images courtesy of Dr. Joao Pippi Salle.



One should not stage a urethral reconstruction using skin or buccal graft if ventral corporotomy and grafting (dermal graft, small intestinal submucosa graft, etc.) is performed. In such cases, rates of graft contraction and loss are high. In these situations, urethral reconstruction using local skin flaps over the grafted area as proposed by Castellan *et al.*[197] is preferred.

3.3.2.4.1 Recommendations

- In summary, recurrence of penile VC is an important problem to recognize after hypospadias repair in childhood and long-term follow-up is mandatory, especially in patients who had chordee repaired initially, whether or not the UP was maintained. The treating urologist should inquire about curvature of erections and erectile satisfaction after puberty. Mild VC can be corrected by midline dorsal plication. Moderate and severe chordee often require more aggressive approaches, sometimes in conjunction with staged urethroplasty.

3.3.3 Fertility considerations in hypospadias

3.3.3.1 Semen delivery

Fertility can be affected in hypospadias due to a host of reasons, yet few studies[198] report fertility or paternity outcomes after hypospadias repair. Hypospadias has been linked to the testicular dysgenesis syndrome and to the spectrum of differences of sexual development (DSD), which are associated with impaired testicular functioning.[199] Whether men with isolated hypospadias are at risk of testicular dysfunction (i.e. impaired steroidogenesis and spermatogenesis) has, to date, been the topic of limited studies.

Male fertility encompasses more than mere spermatogenesis. Several mechanical factors play an important role in achieving fertilization of an egg. In hypospadias, ectopic ejaculation due to a nonterminal urethral meatus, urethral sacculation, chordee, with or without micropenis, may all impair efficient semen delivery to the cervix.[6] Chordee, which is the most common concurrent genital anomaly in hypospadias, may further impair coital penetration. If the curvature is severe, normal penetration can be impacted.[7] Micropenis is defined as a stretched penile length of at least 2.5 SD below the mean for age.[12] It has been estimated that an adult penile length of at least 7 cm is needed for penetrative intercourse.[13] Surgery often serves a limited role in length extension and ART assistance may be required to establish pregnancy.[14]

3.3.3.2 Spermatogenesis

The semen quality of men around the world has been shown to be in decline over the last decades, coinciding with an increase in the incidence of hypospadias.[20-25] Very few studies have explored semen characteristics in this specific population.

The first study was conducted by Bracka[26] in 1989. Among men aged 15 to 24 years with hypospadias, 24.3% demonstrated oligospermia. However, these numbers need to be interpreted with caution, as the study was uncontrolled and over 60% of these men had an associated condition (e.g., cryptorchidism, varicocele, testicular torsion, trauma, or chromosomal abnormalities), and no distinction was made between proximal and distal forms of hypospadias.

Asklund *et al.*[27] examined 108 men born with hypospadias, of which only 19 (17.6%) had additional genital anomalies. No difference in sperm characteristics were found between men who had isolated hypospadias and control men. In men born with proximal hypospadias, all semen parameters except semen volume were significantly reduced compared to controls. Moreover, 13% and 43% of men born with isolated hypospadias and proximal hypospadias, respectively, had used fertility treatment to father a child.[28]

Kumar *et al.*[29] published similar results of 59 and 14 men born with distal and proximal hypospadias, respectively. In this cohort, only men who had proximal hypospadias had reduced semen quality in comparison to controls.

3.3.3.2.1 Recommendations

- Although controlled studies are limited, evidence suggests that men born with proximal hypospadias or with associated genital anomalies are at risk for having reduced semen quality and may require fertility treatments. For such men, prompt referral for fertility treatment should be offered if they are unsuccessful at establishing pregnancy.

3.3.4 Heritability and genetic considerations

3.3.4.1 Heritability

Although the occurrence of hypospadias is sporadic in most cases, several studies revealed high rates of familial occurrence of hypospadias. The proportion of hypospadias cases with at least one other affected family member varies greatly due to the methodological differences of the studies, but it has been estimated at between 4% and 22%.[72] The recurrence of hypospadias correlates with the degree of kinship, hence (male) siblings and fathers are more frequently affected than second- or third-degree relatives. The heritability in first-degree relatives is estimated at 57% to 77%, indicating a strong genetic component. Although predominant paternal transmission was initially suspected, maternal and paternal second- and third-degree relatives have been shown to be equally affected.

In line with the high heritability of hypospadias in first-degree relatives, and based on the concept of testicular dysgenesis syndrome that hypospadias and subfertility may have a common etiology, children conceived through ART as a result of paternal subfertility are expected to have an increased risk for hypospadias. This association has been confirmed, though mainly with the use of intracytoplasmic sperm injection.[73-78] However, these results need to be interpreted with caution, as ART itself is associated with multiple pregnancy, low birth weight, and preterm birth, which also have been linked to an increased incidence of hypospadias.[79] In addition, the impact of birth weight on hypospadias is also illustrated in discordant monozygotic twin pairs, in which the twin with hypospadias, in nearly all cases, has the lowest birth weight.[80,81] However, despite the fact that the indirect impact of ART on the development of hypospadias is hard to establish, evidence suggests that the effect of ART is unlikely to fully explain the association between hypospadias and paternal subfertility.[82]

3.3.4.2 Gene mutations

Androgens play an important role in the development of the male external genitalia and are predominantly produced in the testes in men.[37] Abnormal androgen production or action is therefore strongly associated with incomplete development of the UP and hence hypospadias, as well as with other forms of under-virilization.[38,39] Androgen receptor gene mutations underlie a very broad range of phenotypes, including complete unresponsiveness to androgens, that is, the complete androgen insensitivity syndrome; partial responsiveness to androgens, referred to as partial androgen insensitivity syndrome; as well as mild forms of isolated hypospadias or infertility in otherwise typical men.[40-42]

The production of androgens (i.e., steroidogenesis) is a complex process that requires a series of enzymatic steps to produce testosterone and dihydrotestosterone from cholesterol. Numerous mutations of the genes that encode the involved enzymes are associated with under-virilization, including hypospadias.[43] The most frequently reported enzyme defect in the context of hypospadias is 5α-reductase type 2 (5α-SRD2, encoded by SRD5A2) deficiency. The 5α-SRD2 enzyme defect is responsible for

the conversion of testosterone to dihydrotestosterone in (fetal) genital tissues. Severe biallelic mutations give rise to a typical female phenotype at birth in XY individuals, with marked virilization during puberty through conversion of testosterone in dihydrotestosterone by isoforms of the defective enzyme.[44]

Heterozygous mutations of SRD5A2 have been linked to complex as well as isolated forms of hypospadias.[45-48] Mutations that reduce 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3, encoded by HSD17B3) activity have been less frequently associated with hypospadias. This enzyme mediates the final step in the production of testosterone from Δ4-androstenedion in the Leydig cells, and biallelic mutations have been identified in several XY individuals with severe under-virilization or a typical female phenotype. A link with isolated hypospadias has been established as well.[49-52] Although rare, enzymes involved in more upstream steps of steroidogenesis can also result in hypospadias, generally combined with adrenal insufficiency.[53,54] Altogether, the prevalence of enzymatic defects in testosterone biosynthesis in isolated hypospadias is overall considered to be very low.[55-57]

Mutations in genes involved in differentiation of the bipotential gonad can result in arrest of gonadal development and consequently, gonadal dysgenesis and impaired testicular hormone production. Most often, this will lead to complex genital phenotypes, such as genital ambiguity or a female phenotype at birth. However, recent reports have shown mutations in very mild phenotypes as well. An important example is steroidogenic factor 1 (SF1, encoded by NR5A1), which is involved in the development of both the adrenals and gonads.[58] Although NR5A1 mutations were initially reported in XY females or XY males with severe under-virilization (e.g., a combination of hypospadias, cryptorchidism, and short penile size), heterozygous mutations have now been found in infertile men with normally developed genitalia.[59-61] This broad phenotypic spectrum has been hypothesized to be caused by multiple hits, that is, a combination of heterozygous NR5A1 mutations with potentially deleterious variants of other DSD-related genes.[62] Under-virilization and testicular dysfunction was reported in heterozygous mutations of the GATA4–FOG2 tandem, which plays an important role in early testicular development.[63,64]

Similar to NR5A1, mutations in WT1, generally causing syndromes with complex genital phenotypes (e.g., Denys-Drash, Frasier, and WAGR syndrome), have been identified in boys with isolated hypospadias as well.[65,66]

The number of genes associated with isolated hypospadias is rapidly increasing.[67-71] It is therefore likely that further research, especially in familial cases, will unravel more genes or combinations of genes which, when mutated, can result in a broad phenotypical spectrum.

3.3.4.2.1 Conclusion

- Several genetic defects associated with testosterone biosynthesis disorders and disorders of gonadal development can become manifest at birth as isolated hypospadias. As most of these genes are important for gonadal development, maintenance, and function, it is expected that such mutations may result in impaired testicular functioning later in life. However, most isolated hypospadias cases are idiopathic and with an unpredictable outcome with regard to gonadal function and fertility.

3.3.5 Psychosocial considerations

Carmack and colleagues[200] note that medical intervention has not always been advisable. They quote from a 1917 textbook that states, "Many patients have [glanular hypospadias] without being aware of the fact, while the greatest inconvenience it produces is a slight imperfection in erection and a dribbling at the end of urination." Surgical repair of hypospadias, especially the milder cases, is not necessary for a boy's survival or urinary functioning.

Many men have mild or distal hypospadias without being aware it could be a medical issue. Fitchner and colleagues[201] in Germany analyzed the meatal location of 500 "normal" men and found that only 275 men (55%) had a meatus located at the very tip (distal third) of the glans. The team observed that "it remains unclear whether the tip of the glans [penis] is truly the normal site" for the urethral opening. The authors also questioned whether surgical "correction" of hypospadias was necessary, given what they admitted were the "significant complication rates" of "reparative" surgeries.

Why is hypospadias regarded as being "important" enough to warrant surgical intervention and risk a relatively high complication rate for an elective procedure? The rationale for surgical intervention has been founded upon the Freudian belief that a) growing up with a hypospadiac penis will lead to negative psychosocial effects for the person concerned, including stigma, shame, teasing, and bullying; and b) that an intervention ameliorates the presumed effects.[202] There are also the commonly held notions that children do better with hypospadias surgery performed before the advent of conscious memory and that complications rates are lower in children.[203]

Roen and Hegarty[202] remark that no medical survey has ever examined the psychological impact of being able to urinate while standing, as other aspects of surgery are typically assessed in the medical setting. Somewhat related, research[202] points out the anxiety surrounding public urinals and how threatening it is for some men to urinate in that context. Studies[204] also indicate that many men sampled from the general population live with hypospadias in varying degrees and are not concerned by their genital difference. Dodds and colleagues[204] surveyed 56 men who were identified as having hypospadias by a urologist during an appointment for another urological issue, providing the most comprehensive data regarding the outcome of uncorrected hypospadias. The authors remarked that some of the men were only aware of their hypospadias because a healthcare professional had mentioned it to them. More than 95% of the men were sexually active without difficulty and only 5% preferentially sat to void. The vast majority (95%) did not have issues with their genital appearance and only one man expressed an interest in surgery when asked.

In a second study, Schlomer and colleagues[205] conducted an online survey of 736 adult men who completed a series of self-reported questions about the appearance of their penis and were asked to select diagrams that resembled their situation. If the men selected a diagram that showed a urethral opening located at the proximal one-third of the glans and/chose a foreskin that aligned with the typical appearance of the foreskin of men with hypospadias, they were considered to have possible untreated hypospadias. Fifty-two men (7%) of the sample self-reported as having hypospadias. In that same study, researchers asked men about how often they sat to urinate and the extent to which it bothered them. No significant differences were found between the control and hypospadias groups.

Qualitative research on adults with atypical sex development suggests that the processes involved in medical care may exacerbate the psychological effects of the condition itself. Patient narratives, including those of men who had had hypospadias surgery, demonstrate that experiences of early intervention and clinical management can lead to feelings of devaluation and feeling discredited as human beings.[206] Children and young adults who are operated on are especially vulnerable to repeated genital examinations and possible photography, because doctors are compelled to follow up on results. Genital surgery is intended to "normalize," but the attendant scrutiny by medical providers that follows genital surgery is not experienced as "normal" and acts as a direct challenge to the psychological justification for surgery.[207] Creighton and colleagues[208] and Meyer-Bahlburg and colleagues[209] showed that medical and genital examinations can be experienced as stigmatizing, and that real and perceived stigma experiences and related anxieties may add up to a general sense of being abnormal in terms of body image or even overall self-image, and can become internalized. The tendency toward internalization appeared to be particularly strong in adolescence, whereas later in adulthood, at least some participants appear to develop more of a disregard of the opinions and reactions of others.[209]

Additionally, there is some concern that "corrective" surgery on infants is performed without their consent, and therefore infringes on the rights of children and their bodily integrity, as the surgery is not always medically necessary. Bodies such as Human Rights Watch[210], the United Nations[211], Amnesty International[212], and the European Union Fundamental Rights Agency[213] all share this concern. Parents are often faced with conflicting options of wanting to "normalize" their children and preserve their options for the future.[214] Healthcare professionals are under a great deal of pressure to ensure that diagnostic information is accompanied by offers of some form of "normalizing" solution.[207] Although this may help contain the anxiety of physicians and patients/parents, such action also comes with the subtext that body differences are unacceptable. It is this subtext that may ultimately be unhelpful and counterproductive from the points of view of those seeking to build positive identities and communities around notions of biological sex diversity.[206]

Jones and colleagues[215] surveyed 52 adolescents (13–15 years old) who had hypospadias surgery as children. The authors found an association between recollection of surgery and dissatisfaction with body appearance. Those who recalled going through the process (i.e., those older than 5 years at the time) reported poorer body-image satisfaction. Unfortunately, the authors lacked body satisfaction scores from a control group of adolescents with hypospadias who did not undergo surgery, and it is unclear from the retrospective data if the memory of the event was modified by other factors or by caregivers.

3.3.6 Long-term sexual quality of life

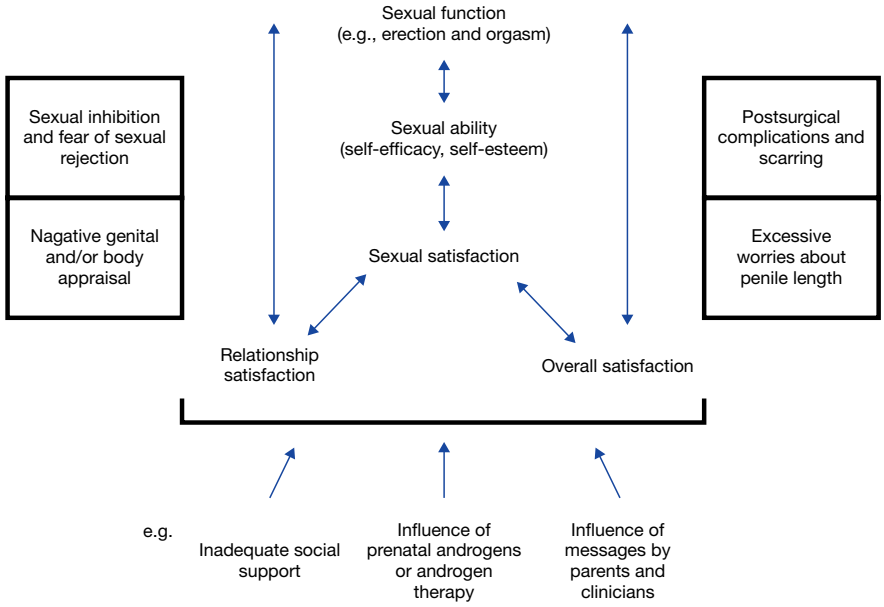
Sexual challenges in adults who underwent hypospadias surgery may take many forms, including penile image issues due to a history of genital surgery and genital scarring, residual or recurrent penile curvature and complications, possibly causing cosmetic and functional difficulty, including erectile dysfunction, ejaculatory problems, and perhaps also loss of genital sensitivity.

Ultimately, it remains difficult to determine to what extent physical, psychological, and social aspects influence sexual experiences, because these factors cannot be investigated independently. **Figure 3-8** illustrates an interactive and dynamic biopsychosocial model of sexual quality of life affected by many factors, including psychological effects, such as impaired psychological wellbeing in addition to social and sexual anxieties, social stigmatization, traumatic treatment experiences, emotional, cognitive, and body image development; biological effects, genetic effects, or both, possibly affecting libido; and social effects, such as inadequate peer support, social isolation, and parental anxieties about the boys' future, which might result in overprotection and may limit the patients' development of autonomy and self-confidence.

With the presence of any chronic birth condition, the risk of a disturbed psycho-emotional and social development is increased, as parental anxiety, invasion of personal privacy, pain or physical discomfort, frequent hospitals visits, and early or late physical development may all lead to patients feeling being "different" from their peers. Any differences in social and sexual dimensions found in these children and adults with hypospadias would need to be explained within a biopsychosocial framework that could take account of the transactions with the social systems of hospital, school, or work, family and friends, the type of condition, bodily presentation, and treatment demands.[216] Ultimately, a linear model in which psychosexual and social outcomes are hypothesized to be directly determined by the genital difference and surgery proves to be an oversimplification.

FIGURE 3–8
An Interactive and Dynamic Model of Sexual Quality of Life Within a Biopsychosocial Framework in Men With Hypospadias

Adapted from: *Schober JM. Sexual quality of life in an intersexual population: a needs assessment.* BJU Int. *2004;93(Suppl 3):54–56.*



3.3.6.1 Psychosocial and psychosexual outcomes following surgery

The social and sexual life of adults operated for hypospadias during childhood has been studied by a few authors. Psychosocial and psychosexual outcomes following genital surgery are of particular importance, and investigations[218,219] have been called for by advocacy groups and human rights groups since the 1990s.

In a quality-of-life study of 77 boys (aged 7–17 years), Schönbucher and colleagues[220,221] examined a range of factors relating to quality of life, adjustment, development, surgical outcome, and timing of hypospadias surgery, and they used a control sample of boys who had undergone hernia repair surgery. The authors concluded that there was no significant difference between the 2 samples on various measures concerning the boys' gender role behaviour, first sexual experiences, sexual attitude, and how they perceived their penises. First sexual intercourse was found to occur at the same age, which corroborates other studies reporting that the mean age of sexual debut is similar for adolescents with and without hypospadias.[221] However, boys and adults with childhood hypospadias repairs were more likely to have a greater fear of sexual contact and inhibitions related to nudity.[222]

Although limited, the existing evidence does not point to a poorer wellbeing in boys with hypospadias, nor that surgery is likely to improve their wellbeing. In a substantial meta-analysis[221] of 13 studies, the same research group concluded, "Guidelines for surgical treatment are partly based on psychological assertions that have not been empirically confirmed."

Although some studies show that adult men can experience sexual pleasure and orgasm after hypospadias surgery, complaints about weakness of the ejaculation or the need to milk semen out of the urethra, as well as erectile problems, seem to be more common compared to controls.[223,224] Feelings of social isolation and lower self-esteem have been described in men with childhood hypospadias repair.[225,226] Additionally, men with hypospadias report fewer sexual partners than those without hypospadias, but are just as likely to be in a stable sexual relationship.[226]

3.3.6.2 Sexual satisfaction

Regarding sexual satisfaction, men satisfied with their surgical outcome were also more likely to be satisfied with their sexual life.[227,228] Compared to those who had childhood circumcisions for phimosis in a country where this practice is not routine, both groups were able to live a satisfactory sexual life. Minor differences observed between groups were not related to the circumcised appearance of the penis, even in cultures where circumcision is uncommon.[227] The severity of hypospadias and the number of prior hypospadias operations do not appear to impact psychosexual outcomes. Psychosexual adjustment, measured by the Minnesota Multiphasic Personality Inventory, did not vary by these factors.[222] When the same questionnaire[229] was administered to all men from Tuscany entering the Italian national military service, those with hypospadias (both repaired and not repaired) were found to have difficulties in contacting women and fewer had experienced intercourse, although they all rated sexual function as normal.

3.3.6.3 Concern over cosmesis and effect on sexuality

Hypospadias surgery may also result in concerns about cosmesis.[222,230] Studies using self-reported questionnaires about satisfaction with the cosmetic result indicate that one-third of the men with hypospadias consider their penile appearance abnormal compared to peers of the same age, even if surgery is meant to "normalize" their genital appearance. Adolescents with prior hypospadias repairs are most bothered by the perceived decreased penile length than any other physical factor, such as scar, circumcised appearance, meatal position, or residual chordee.[223,228] However, children reported a better perception of penile cosmesis than their parents or surgeons did.[231] Nonetheless, adults with prior hypospadias repair continue to suffer from negative genital perception.[232] Interestingly, however, appearance of the glans and position of the meatus are not necessarily the predictors of

dissatisfaction.[231] Rather, penile length seems to predominate as the most important factor relating to satisfaction with both penile appearance and sexual function.[233] In one Swedish study[182], penile length was significantly shorter in men with hypospadias. Anderson[234] reported that patients with proximal hypospadias had significantly more dissatisfaction compared to controls regarding their penile length, as well as feeling greater uncertainty regarding physical contact. In men, excessive worry about penile size and concerns over masculinity have been found to contribute to poor self-esteem and negative psychosocial outcomes. Liu[235] observed that nearly half of adult patients with hypospadias complained that their penis had been ridiculed by partners. As mentioned above, penile length is not a surgically modifiable variable.

These concerns underscore the importance of long-term follow-up of patients with hypospadias in order to confirm initial positive outcomes.

3.3.6.4 Parental decisional regret

Recent studies[236] report increasingly on parental distress or remorse after their decision for hypospadias surgery. Some studies[237] indicate that 39% to 58% of parents feel mild to strong decisional regret after elective hypospadias surgery for their sons. Decisional regret was unrelated to parental desire to avoid circumcision, duration of follow-up, or development of complications. Parental regret was also expressed by many parents of children who did not experience complications. The authors thereby concluded that aiming to minimize surgical complications and providing parents with better counselling about presurgical expectations might be effective ways of reducing parental regret. However, they did not discuss whether the surgery was necessary in the first place, nor whether choosing not to intervene via surgery could reduce or even eliminate the potential for future parental regret.

These data do not suggest surgery is the optimal treatment for ameliorating stress in parents of young children with atypical genitalia; however, it does illustrate the need for parents to receive help to deal with their potential negative reactions and expectations. Those who choose surgery may be motivated by the expectation that surgery will normalize their child's genital appearance and spare the child from any ridicule or rejection. Families may have unrealistic expectations regarding the extent to which such interventions will relieve their distress and improve the quality of life for the child and family.[238] They may also believe that their concerns about sharing information about the child's "difference" with others (friends, families, the child) will dissipate. Normalizing surgery does not eliminate psychological engagement with these issues.[203] Failing to offer adequate psychosocial support to parents making irreversible decisions about surgery can raise significant ethical and legal concerns. Families may not only experience regret when they make decisions based on limited or biased information, but their children's autonomy and integrity is also not considered when they are not involved in the decision-making.[238]

3.4 Summary of Recommendations

3.1.2.3.1 Sexual function in males: medical and functional considerations

- Erectile quality, penile sensation, and ability to ejaculate and achieve orgasm should all be investigated, documented, and treated in men with SB, if developmentally appropriate and desired by the patient.

3.1.5.1 Sexual function in females: medical and functional considerations

- Sex therapy specific to SB has been recommended to limit obstacles to fulfilling sexual lives. Patients with SB should be counselled on prevention of sexually transmitted diseases and pregnancy. As several patients are latex-positive, they should be informed about using latex-free condoms.

3.1.8.2 Recommendations for fertility and pregnancy in females with spina bifida

- Women or their male partners with a personal NTD history or a previous NTD pregnancy are considered high risk, and they require a diet of folate-rich foods and a daily oral supplement of 4.0 mg folic acid beginning at least 3 months before conception and until 12 weeks' gestational age.

3.2.13.1.1 Recommendations for menopause

- During menopause, appropriate screening and treatment by a bone health specialist should be considered.

3.3.2.4.1 Recommendations for chordee and curvature

- Recurrence of penile VC is an important problem to recognize after hypospadias repair in childhood and long-term follow-up is mandatory, especially in patients who had chordee repaired initially, whether or not the UP was maintained. The treating urologist should inquire about curvature of erections and erectile satisfaction after puberty. Mild VC can be corrected by midline dorsal plication. Moderate and severe chordee often require more aggressive approaches, sometimes in conjunction with staged urethroplasty.

3.3.3.2.1 Recommendations for fertility considerations in hypospadias

- Although controlled studies are limited, evidence suggests that men born with proximal hypospadias or with associated genital anomalies are at risk for having reduced semen quality and may require fertility treatments. For such men, prompt referral for fertility treatment should be offered if they are unsuccessful at establishing pregnancy.

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C4

Complications in Adulthood for Patients With Pediatric Reconstruction

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Complications in Adulthood for Patients With Pediatric Reconstruction

4.1 Introduction

Increased numbers of patients with pediatric genitourinary reconstruction are now living into adulthood. However, caring for adult patients with reconstructions can be challenging for providers. Reconstruction may have occurred decades before, with surgical records no longer available, and patients and their families may be unaware of or unable to recall the procedures that were performed. Furthermore, cognitive decline in populations such as in patients with spina bifida (SB) may add to these challenges. Changes in patients' body habitus and loss of function may also contribute to problems with previous reconstructions.

In this chapter, we present recommendations for the management of unique issues faced by adult patients with congenital neuropathic bladder. Due to the limited number of studies on the treatment of such patients, many of these recommendations are gleaned from available data on adult patients with spinal cord injury (SCI)—a more commonly studied population—or pediatric urologic literature. This chapter also discusses the evaluation and management of complications in, and secondary to, reconstructions, and the long-term risk for malignancy in patients with congenital neuropathic bladder.

4.2 New or Escalating Recurrent Urinary Tract Infections

Urinary tract infections (UTIs) are a major source of morbidity in patients with congenital neurogenic bladder (NGB).[1] For the purposes of this chapter, "new" UTIs indicates patients without a significant history of UTIs, but who then develop several UTIs over a short time span; and "escalating" UTIs indicates patients with a history of UTIs who then begin to experience an increase in the severity of symptoms, hospital admissions, or other sequelae (eg, sepsis).

New or escalating UTIs in adult patients with NGB may indicate underlying problems, such as new-onset urinary obstruction, and can also directly damage the long-term health of the kidneys.[2] Adult NGB patients may be at increased risk for UTIs due to persistent bacteriuria, resulting from factors such as incomplete bladder emptying, use of clean intermittent catheterization (CIC) or chronic indwelling catheters, or interposition of bowel within the urinary tract. Given the heterogeneity of underlying problems and the absence of existing robust guidelines or studies, significant variations exist in both the diagnosis and treatment of UTIs across centres that treat adult patients with NGB.[3]

4.2.1 Care and status of the urinary tract

As patients with congenital genitourinary conditions transition from pediatric to adult care, providers must understand that these patients—with near-universal chronic bacterial colonization of the urinary tracts and bacteriuria—represent a different population from otherwise healthy patients with a UTI. The framework of care for patients with genitourinary reconstruction depends on each individual's bladder management and urinary tract functional status: some individuals will void spontaneously, while others have had extensive and possibly multiple reconstructive procedures to increase bladder capacity and compliance. Many patients (76.8% of adult patients with SB), however, need to self-catheterize—either via the urethra or a continent catheterizable channels—in order to empty their reservoir.[4]

4.2.1.1 Research limitations

A major challenge in preventing and treating UTIs is insufficient research and data for analysis in adult patients with congenital NGB. Recently, the Neurogenic Bladder Research Group performed a systematic review to inform best practice policy statements for UTI prevention in adult myelomeningocele (MMC), but data were too sparse for a meta-analysis. Even broadening the search to include all patients with NGB (including those with spinal cord injury [SCI] and multiple sclerosis [MS]) and recurrent UTIs allowed for recommendations; thus, policy statements were generated from a review of the literature on other patient populations with extrapolation to the neurogenic population.[5]

4.2.1.2 Disease spectrum in adults with NGB

Congenital NGB comprises part of a spectrum of genitourinary disorders in childhood, which affects bladder storage and voiding.[6] Patients with SB and bladder exstrophy-epispadias complex (BEEC), arguably, make up the majority of this pediatric cohort who have transitioned into adult care, with a history of urologic reconstruction and/or the need for lifelong urinary tract surveillance. However,

much of the literature regarding adult congenital NGB is most often mixed with SCI due to the much higher prevalence of this condition. Other congenital conditions, such as rhabdomyosarcoma of the pelvis, prune belly syndrome, and posterior urethral valves, make up a small proportion of this patient population. A full review of bladder management considerations for these conditions in pediatric life is contained in **Chapter 2** of this book.

4.2.1.3 Bladder reconstruction

Enterocystoplasty, either augmentation or substitution (with or without a catheterizable channel), is most often performed in childhood to increase bladder capacity and compliance, and to protect the upper tracts from high bladder pressure. A concomitant bladder neck procedure—in the form of a sling, urethral lengthening/tubularization, artificial urinary sphincter, or closure—may also have been performed to improve continence. Currently, most adult patients who underwent a urinary diversion in childhood are continent (as a primary objective is to achieve continence), though older patients may have an incontinent diversion such as an ileal conduit.[2,7]

4.2.2 Epidemiology of UTIs, bacteriuria, and bladder stones in NGB

4.2.2.1 UTIs

The annual incidence of UTIs in all adult patients with NGB (including SCI) may be as high as 20%, with almost 50% of children with SB having more than five UTIs by 15 years of age.[8] Estimating the incidence of UTIs in adults with NGB is more difficult for two reasons: firstly, the small population and, secondly, the heterogeneous definition of UTIs.[8] Despite these limitations, it is well documented that UTIs present a prominent source of morbidity, ranging from local infectious sequelae to significant sepsis, and end-organ dysfunction.

4.2.2.2 Risk by type of augmentation

Traditionally, it has been thought that the colon, which secretes more mucus, may be at higher risk for UTIs and stone formations than the ileum. This theory appears to be refuted in a large, contemporary retrospective review of pediatric patients with BEEC who underwent continent reconstruction; no difference in ileum versus colon (30% vs 28%) for the development of bladder calculi was evident.[9] Interestingly, the status of the bladder neck was not found to be an independent risk factor. Only four patients underwent colonic neobladder, of which one patient, representing 25% of the group, had pyelonephritis (odds ratio [OR], 2.5), compared with 6% of patients in the combined ileal and colonic augmentation group; there was no significant difference in the type of bowel.[9] No stones or pyelonephritis developed in patients with gastrocystoplasty; however, significant hematuria-dysuria syndrome did occur. While the acidic pH of urine in a gastrocystoplasty may reduce the risk of bacterial colonization and confer the advantages of fewer UTIs and/or bladder stones,[10,11] the clear disadvantages of severe metabolic imbalances, malignant risk, and hematuria-dysuria syndrome—that can cause significant pain, bladder spasms, and gross hematuria—have seen gastrocystoplasty fall out of favour.

4.2.2.3 Bacteriuria

Augmented bladders using bowel will almost uniformly be chronically colonized with bacteria, complicating the ability to accurately distinguish asymptomatic bacteriuria from true UTIs. Intermittent catheterization also promotes bacteriuria; thus, how much the presence of bowel in contact with the urinary system, or the introduction of a catheter, influences bacteriuric potential is not well delineated.

4.2.2.4 Bladder stones

Both large and small bowels produce mucus that may contribute to chronic bacteriuria as well as stone formation, the latter being the most common complication requiring operative intervention after cystoplasty.[10] Although historical series have estimated bladder stone development to be greater than 50% after augmentation, recent large, retrospective reviews of pediatric patients have found the rate to be much lower (9%–15%).[13-16] Of note in these series, the type of bowel segment used did not impact the rate of stone formation. Some authors have postulated that catheterization via the Mitrofanoff channel increases the risk of stone formation compared with urethral CIC.[10] A large series demonstrated that recurrent UTIs and a primary diagnosis of BEEC were the only independent risk factors for developing bladder stones.[15] The predominance of struvite in bladder stones, indicating that an infective etiology might play a strong role in formation, has also been challenged. Another large series reported 31% of bladder stones in patients with NGB were noninfective; interestingly, those that were considered "infection stones" (eg, struvite, calcium phosphate, ammonium urate) were not associated with recurrent urea-splitting organisms, neither were factors such as bladder neck procedure or a catheterizable channel.[17]

In a contemporary cohort of adult SB patients, Liu *et al.* found that the most common urologic procedure performed was urinary tract stone treatment (26.7%). However, approximately 80% of these procedures were noted in adult patients compared with only 19.6% in pediatric patients.[7] Interestingly, a minority of the procedures (31%) were performed for bladder stones, and the remainder were for ureteral or renal stones.

4.2.3 Severity of postoperative infections

The combination of UTIs and urolithiasis means that postoperative infections may be particularly severe in the adult NGB population. Wang *et al.* found in a large US insurance claims dataset that SB patients had a 2.5 times increased risk for UTIs after upper-tract stone surgery and a 2.7 times increased risk for sepsis.[18] In a 2017 retrospective cohort study of patients undergoing ureteroscopy (34 patients with NGB vs 368 control patients), Stauffer *et al.* found the rate of postoperative febrile UTIs was 9% in patients with NGB compared with 1.4% in controls. Furthermore, patients in the series who voided without CIC did not experience postoperative febrile UTIs; only patients performing CIC as a bladder management technique (p=0.01) experienced postoperative febrile UTIs.[19] One final relevant finding from this series was that 80% of those with febrile UTIs had a different organism than originally cultured preoperatively; this indicates appropriate preoperative clearance, but highlights the difficulty in sterilizing the urine of patients with chronic bacteriuria, stones, and/or indwelling tubes.[19] The American Urological Association Guidelines on antimicrobial prophylaxis for

upper-tract instrumentation recommend sterilizing the urine, if possible (which indicates culture-directed therapy), and possibly extending the course of prophylaxis for more than 24 hours when sterilization is not possible.[20]

4.2.4 Inappropriate treatment of asymptomatic bacteriuria

In the age of antimicrobial resistance, treatment of asymptomatic bacteriuria poses a significant risk to patients with congenital NGB. Bacteriuria in an otherwise asymptomatic patient with NGB is expected, and should not be treated. However, diagnosis of UTIs in patients with NGB can be challenging in a setting of vague symptoms or isolated fever, given the near-universal presence of bacteriuria, often in an insensate patient. Patients with impaired sensation from spinal cord diseases often experience atypical symptoms associated with infection, such as headache, irritability, nausea, or fatigue. By extrapolating data from the SCI population, including at specialized rehabilitation facilities, it was found that asymptomatic bacteriuria was treated in more than 50% of cases when the bacterial load and leukocyte count were deemed significant.[3] The dangers of overtreatment include antibiotic resistance, adverse effects from an individual antibiotic, secondary overgrowth (including fungal infections), and *Clostridium difficile*; there are also emerging data suggesting a possible increased risk for stones due to antibiotic exposure.[21] In populations with increased susceptibility to stone formation, antibiotic stewardship and careful thought regarding treatment of any suspected UTI should be exercised. Providers should take care to know the specific signs of infection for each individual patient, and in the absence of symptoms or planned intervention, routine urine screening for bacteriuria should not be undertaken.[22]

4.2.4.1 Recommendation

- Routine screening for bacteriuria in the absence of symptoms should not be undertaken. Exceptions to this include patients who will undergo invasive procedure, or endoscopic or open surgery of the urinary tract—these patients should have a urine culture taken prior to any procedure, given the high likelihood of bacteriuria **[Level of Evidence (LOE) 1; Grade of Recommendation (GOR) A-B]**.

4.2.5 Diagnosis of acute UTIs

If a UTI is suspected, a urinalysis and urine culture should be taken prior to initiation of antibiotic therapy; once culture has resulted, therapy should be changed if necessary.

There are no evidence-based cutoff values for laboratory values (ie, urinalysis and urine culture) for the adult NGB population.[23] Using pediatric guidelines, the American Academy of Pediatrics (AAP) defines UTIs as 5 x 10^4 colony-forming units per mL (CFU/mL) by suprapubic aspiration (SPA), while the European Association of Urology/European Society for Paediatric Urology define UTIs several ways, depending on mode of collection (10^3–10^5 catheterized; void >10^5 with no symptoms, or >10^4 with symptoms; any bacterium present if from SPA).[24,25] In adults with NGB, the most widely used definitions in the literature are consistent with the National Institute on Disability and Rehabilitation Research definition: 10^5 CFU/mL of a single organism, with at least one symptom.[5,26] Importantly,

symptoms typical of UTIs in the non-NGB population (ie, suprapubic pain, dysuria, frequency) may not be the same as those in the NGB population, and it is paramount for the practitioner to be cognizant of this during evaluation.

Patients with genitourinary anomalies who develop recurrent UTIs and who do not have a history of UTIs should be seen by a urologist to investigate the etiology. Patients who escalate from afebrile or infrequent infections to increased frequency or severity of infections (ie, hospitalization, end-organ dysfunction) should be evaluated on an urgent basis also. It is important to differentiate persistent infections versus re-infections, as the former signals an inadequate clearance of the initial infection. New bladder stones are often a sign of worsening urinary tract status, and may represent inadequate emptying of the reservoir, mucus build-up, or a preponderance of ammonia-producing bacteria.

In the acute setting, the choice of empiric antibiotics should be determined by local resistance patterns and antibiograms, as well as the patient's urine-culture history, recognizing the increasing prevalence of multidrug-resistant (MDR) strains. In general, lower-tract UTIs (eg, cystitis, nonfebrile) may be treated for 3 to 5 days, while treatment for upper-tract UTIs (eg, febrile, pyelonephritis) should be extended to 7 to 14 days.[25]

4.2.5.1 Recommendation

- A urine culture should be obtained to allow antibiotic treatment to be tailored for symptomatic UTIs in patients with NGB **[LOE 3; GOR C]**.

4.2.6 Evaluation for recurrent UTIs

The definition of recurrent UTIs in patients with NGB is unclear. However, recurrent episodes of urosepsis, or new or increased frequency of lower-tract UTIs, warrant evaluation. Most importantly, new urinary tract obstructions, which may lead to severe febrile UTIs and progressive renal damage, must be promptly evaluated and addressed.

4.2.6.1 Physical exam, history, and laboratory data

First step in evaluating recurrent UTIs is to perform a thorough physical exam and obtain a microbiological history, as well as review all available laboratory data (including previous cultures). Unlike the general population, where *Escherichia coli (E. coli)* and *Klebsiella* are predominant pathogens, NGB patients tend to have infections with less common pathogens, such as *Pseudomonas*, multiorganism infections, and MDR bacteria. For example, one study in pediatric patients with SB demonstrated a higher likelihood of non–*E. coli* infections compared with age-matched controls (64% vs 41%), and an overall higher infection rate with MDR organisms in pediatric patients with SB (21% vs 10%).[27] In addition, this study demonstrated a 10-fold increase in urosepsis among pediatric patients with SB, with 57% of events caused by MDR organisms.[27] Among pediatric patients with SB, prior reconstruction of the urinary tract did not alter the risk for MDR infections. The urinary flora may change as patients age, and no robust studies have been conducted to date to isolate the most common bacterium in adult patients with NGB who have a history of bladder reconstruction.[6]

As noted previously, a majority of patients with SB manage their bladders using CIC. In all patients with congenital NGB, an increase in the frequency of UTIs should raise suspicion of a failure in compliance of catheterization or an inability to empty the bladder completely. A voiding diary or catheterization chart with recorded volumes may be helpful; if the patient is able to void, a uroflowmeter and postvoid-residual urine test may be used in an office/outpatient setting. Direct observation of the patient's catheterization technique by a provider skilled in CIC education can be helpful to identify opportunities to improve technique, hygiene, and use of equipment.

4.2.6.2 Imaging

Regular (annual) imaging is indicated for all patients. Patients should also be clearly counselled that if they develop recurrent UTIs or an escalation in UTIs, their urology team should be notified, as further imaging may be necessary. Renal and bladder ultrasound can evaluate the upper urinary tracts for dilation; the kidneys and bladder for stones; and for any other changes. If technical or anatomical factors preclude reliable ultrasonography, cross-sectional imaging may be warranted. CT scans without contrast permit more accurate stone evaluation, particularly in the setting of sepsis, to assess for obstructing ureteric stones, which require emergent intervention.

4.2.6.3 Invasive Testing

Endoscopic evaluation of the urinary reservoir is important when evaluating patients with new or recurrent UTIs to rule out pathology, and irrigation of retained mucus may also be beneficial. Urodynamic study (UDS) of the bladder, reservoir, or conduit should be considered if radiologic evaluation and cystoscopy fail to identify a source of infection, particularly if the patient reports new or worsening symptoms, including urinary incontinence.

UDS may identify concerns such as poor compliance or detrusor sphincter dyssynergia (DSD) that exposes the urinary tracts to high pressures, which can result in secondary vesicoureteral reflux (VUR), formation of bladder diverticula (pouch), and/or chronic dilation of the upper urinary tracts. Dysfunctional voiding promotes stasis and hinders the naturally protective mechanisms of voiding. Findings that may be of concern in UDS include a rapid rise in detrusor pressure at low volumes, or an end detrusor leak point pressure (DLPP) greater than 40 mm Hg. In addition, video urodynamics (VUDS) can differentiate many features, including whether reflux occurs during the filling or voiding stage, as well as identifying the bladder volume at which secondary (or pathologic) reflux occurs. If concurrent fluoroscopy is not available, separate imaging with voiding cystourethrogram is appropriate for identifying bladder trabeculation, bladder neck or urethral abnormalities, and VUR. If a patient has had a prior continent diversion, UDS can be performed through a catheterizable channel or the urethra if no bladder neck surgery was performed.

Interpreting UDS results in patients with reconstructions can be particularly challenging, as, for example, leak point pressures depend on the type of reconstruction. When performing UDS, the urinary reservoir should be filled until either leakage, discomfort, or a predetermined maximum capacity volume—based on an individual patient's parameters, or 600 mL as suggested by some authors.[28,29] The largest body of UDS literature on patients with reconstructions exists for augmentation cystoplasty (AC). Bladder storage pressures after AC should remain low; however, instances of poor compliance and/or detrusor overactivity are possible and should be investigated if the patient has had a change in clinical status (ie, UTIs). Quek *et al.* evaluated 26 patients at a mean of 8 years

(range, 4–13 years) following AC and found statistically significant increases in bladder capacity (201 ± 106 vs 615 ± 204 mL) and decreases in end-filling detrusor pressure (81 ± 43 vs 20 ± 12 cm H_20).[30] López Pereira *et al.* studied 32 patients who underwent AC at a mean age of 11 years (2.5–18 years) with UDS at a mean follow-up of 12 years (10–14.5 years). Bladder capacity improvement was more marked at the end of follow-up than at the 1-year UDS after augmentation; however, the filling detrusor pressure did not change over time after surgery.[31]

When a patient is evaluated, the type of bowel segment should also be considered. Gastric and sigmoid pouches are considered to be the least compliant and most contractile, and they offer the smallest capacity.[28] Phasic contractions occurred in 38% of patients at a mean age of 12 years in the López Pereira *et al.* study; contractions were more frequent and at higher pressures with sigmoid colon than with ileum—though this was not statistically significant—and the true meaning of phasic contractions remains unclear.[31] Patients who underwent ureterocystoplasty showed a small bladder capacity and higher mean filling pressure when compared with the enterocystoplasty group.[31]

UDS of a conduit is also possible and should be considered in select situations. The current literature is sparse for ileal or colon conduit diversion performed in pediatric patients with NGB.[32,33] Pressures generated in the ileal conduits of pediatric patients are generally low, but peaks of high pressure can be observed.[34] Knapp *et al.* examined UDS in six patients with ileal conduits to investigate bilateral hydronephrosis. Compared to four control patients with normal upper tracts and conduit leak point pressures of 5 to 20 cm H_2O, Knapp *et al.* identified abnormalities in five of six patients—functional stomal stenosis (2), atonic loop (1), segmental obstruction (1), and high-pressure noncompliant distal segment (1).[35]

Ileovesicostomy is another option that should provide a low-pressure noncatheterizable reservoir designed to minimize complications, if used in a very select group of patients. A small prospective study of UDS results after ileovesicostomy found that the mean DLPP was 8.6 cm H_2O (range, 2–20) in the supine position versus 11.6 cm H_2O (range, 5–25) in the upright position, which was not statistically significantly different.[36,37] In the largest review of outcomes, in 50 patients who underwent ileovesicostomy, Tan *et al.* found 28% of patients were incontinent at the last follow-up.[38] Tan *et al.* reported a decrease in VUR dysreflexia, postprocedure. Mean follow-up was only 26 months from surgery, with an 8% rate of urosepsis and 6% rate of bladder stones, which was an improvement from their reported rates presurgery, but the presurgery rates reflected patients' prior entire life compared with the relatively short-term follow-up period in the postsurgery data. Hellenthal *et al.* reported that all 12 of 12 patients had ongoing complications—recurrent stones (2), infectious issues (7), urethral discharge (1), and required conversion to ileal conduit (2)—at follow-up at 5.5 years.[39] Although a less complicated surgical option, when compared with catheterizable stomas or even ileal conduits, ileovesicostomy should be undertaken in select settings only, due to ongoing surgery-associated complications and lack of rigorous long-term outcomes.

There are conflicting data on whether poor compliance contributes to febrile infections in the population with neurogenic bladder. Esclarín de Ruz *et al.* postulated that poor compliance and DSD were the reasons cervical injury was a risk factor for febrile UTIs in adult patients with SCI.[40] However, in a retrospective review of pediatric and adult patients with SB, Chaudhry *et al.* reported that urodynamic parameters were not associated with frequent febrile UTIs.[41]

4.2.6.3.1 Recommendation

- Endoscopic evaluation and urodynamic testing should be considered in adult patients with congenital NGB who have new or recurrent symptomatic UTIs **[LOE 5; GOR C-D]**.

4.2.7 Medical prevention of UTIs

4.2.7.1 Bladder management

The most important element in any approach to preventing recurrent UTIs in the NGB population is a well-defined bladder management plan. If a patient was previously voiding, careful analysis of residuals and the upper tracts—using UDS—can determine if the patient needs to alter emptying techniques to reduce risk for UTIs. Incomplete emptying may promote an ascending UTI. Despite the known risks for bacterial inoculation with initiation of CIC, the risk for infection may be greater with persistent incomplete emptying, leaving CIC as the safer alternative.[22] For patients already practising CIC, their catheterization technique should be optimized; this may include adjusting the type of catheter or increasing the frequency of catheterization. An indwelling catheter or suprapubic may lead to an increased risk for infection, and thus CIC is the preferable option.

4.2.7.2 Bowel management

Neurogenic bowel may coexist with bladder dysfunction in adult congenital patients due to neurologic dysfunction or an anatomical colorectal anomaly. Chronic constipation substantially impairs bladder function and increases risk for recurrent UTIs; therefore, bladder management plans must include bowel management strategies as well.

4.2.7.3 Prophylactic oral medications

Prophylactic antibiotics for the prevention of recurrent UTIs in adult patients with NGB have shown no long-term benefit in the reduction of symptomatic infections, and are associated with the development of antibiotic resistance.[5,42-44] Despite the lack of documented benefit, Wiener *et al.* found within data from the US Centers for Disease Control and Prevention's National Spina Bifida Registry that the daily use of antibiotics was greater in adult patients with SB than pediatric patients with SB (17% vs 12%).[4] Although routine antibiotic prophylaxis is not recommended, due to low efficacy for symptomatic infections, there may be a role for antibiotic prophylaxis in select patients who experience recurrent or severe UTIs (despite urologic optimization), or for whom the risk for infection is especially severe (eg, immunocompromised patients).[45]

Oral methenamine salts work by producing bacteriostatic formaldehyde in the urine from hexamine,[46] thus avoiding the problems with antibiotic resistance. However, a 2012 Cochrane review concluded that there was a lack of efficacy for UTI prevention in patients with NGB or renal tract abnormalities.[47]

4.2.7.3.1 Recommendations

- Routine antibiotic prophylaxis is not recommended due to its low efficacy in preventing symptomatic infections and risk for antibiotic resistance **[LOE 2; GOR B]**.

- Methenamine salts have not been found effective in the NGB population; therefore, they are not recommended **[LOE 2; GOR C]**.

4.2.7.4 Intravesical irrigation and medication

The best data on the use of intravesical saline irrigation come from a study by Husmann.[45] A significant decrease in both bladder stones and UTIs over a 10-year period was found in patients compliant with 240 mL of weekly irrigation compared with lower-volume irrigation. Intravesical treatment with a variety of other agents has been described in the literature. Kanamycin colistin decreased bacteriuria in adult patients with SCI,[48] while neither saline, acetic acid, nor neomycin-polymyxin instillations provided any benefit in patients with indwelling catheters.[49] The safety of gentamicin instillations and minimal systemic absorption make this the best-documented intravesical preventative antibiotic instillation,[50,51] with retrospective data showing a decrease in symptomatic UTIs in adult patients with NGB[52]; however, randomized controlled studies are lacking and the long-term auditory risk, with even minimal systemic absorption, has not been well studied.

4.2.7.4.1 Recommendation

- Intravesical irrigation with at least 240 mL of saline irrigation, or intravesical instillations with gentamicin, can be used on a short-term basis in patients with NGB for symptomatic UTI prevention, though other agents cannot be recommended **[LOE 4; GOR C-D]**.

4.2.7.5 Probiotics

Newer areas of study have focused on nonantibiotic-driven methods to reduce the incidence of UTIs, without promoting antibacterial resistance. In this vein, probiotics have been identified as a potential prophylactic due to their ability to alter the microbiome of a host. These probiotics may be delivered either orally or via intravesical instillation. A 2017 Cochrane review identified a total of three small studies, involving 110 patients, looking at intravesical instillation of low-virulent *E. coli* to reduce the risk for symptomatic UTIs in patients with NGB bladder.[53] It is uncertain whether instillation of *E. coli* does reduce the risk for symptomatic UTIs and how this may apply to adult patients with congenital NGB.

There is no existing evidence for oral probiotic use in the adult NGB population, but a prospective multisite randomized controlled trial (RCT) is currently studying the effectiveness of oral probiotics (*Lactobacillus*) in preventing UTIs in patients with SCI.[54] Patients with a known history of bladder reconstruction or surgical intervention are excluded from this cohort; however, it may be possible to glean important lessons from this trial that can be applied to the adult congenital population.[54] Probiotics may be particularly advantageous as the role of bacterial interference would potentially curb the use of antibiotics and lessen the degree of resistance in these at-risk patients. Use of probiotics may be limited by fecal incontinence in some individuals with neurogenic bowel and bladder, and follow-up with patients who are put on probiotics for this side effect is necessary after initiation of a new oral probiotic regimen.

4.2.7.6 Other oral supplements

Oral supplements designed to target the urinary tracts, such as cranberry and D-mannose, are often used for UTI prevention in the non-neurogenic population, but they do not seem to be effective in the NGB population. Two large double-blind RCTs (largely consisting patients with SCI or MS) showed no benefit, while results from smaller studies in pediatric SB patients were mixed.[5,55] The pathogens targeted by D-mannose and cranberry derivatives are *E. coli* and *Pseudomonas,* which may account for the lack of efficacy in NGB patients because their infections tend to comprise varied pathogens compared with UTIs in women with normal bladders. Despite a perceived lack of benefit, larger trials focusing specifically on SB patients and/or patients with a reconstructed bladder may provide better insight into potential efficacy of these agents.

4.2.7.6.1 Recommendation

- There is no evidence to support the use of cranberry derivatives or D-mannose in the adult NGB population **[LOE 1; GOR A-B].**

4.2.7.7 Surgical treatment

Surgical treatment to address new or escalating UTIs should be tailored to the patient. For example, a patient with infrequent bladder drainage due to an inability to effectively perform urethral catheterization may benefit from having either urethral reconstruction or a Mitrofanoff channel. As another example, a patient with escalating or recurring urinary infections who has been diagnosed with bladder stones may benefit from cystolitholapaxy. Patients who have undergone reconstruction in childhood pose particular challenges as their anatomy has already been altered.

Injection of onabotulinumtoxinA (Botox®) has been described as a therapeutic option to prevent UTIs by lowering detrusor pressures. A retrospective multicentre study of 214 patients with SCI, MS, and SB found a significant long-term reduction in UTIs after Botox injections.[56]

In patients with high bladder pressures or poor emptying, but where CIC (with or without reconstruction) is not possible, incontinent options such as vesicostomy, ileovesicostomy, or ileal conduit may be performed. A suprapubic catheter can be considered for patients who are unfit for more extensive surgery.[57] In a study of pediatric MMC patients who had very high-pressure bladders and few other options, nine patients underwent incontinent ileovesicostomy for worsening UTIs or progressive hydronephrosis, with only one febrile UTI in follow-up. However, follow-up was limited in this series.[37]

4.3 Continence Challenges

4.3.1 Continent catheterizable channels

Functional reconstruction of the lower urinary tract requires three components:

1. A reservoir that stores urine with adequate capacity;
2. A continence mechanism that also allows for efficient bladder emptying; and
3. A means of draining the urine.

In patients with neurogenic lower urinary tract dysfunction, associated neurological limitations in mobility and/or dexterity can lead to difficulty accessing the native urethra. These limitations are often addressed successfully with a continent catheterizable channel, which makes abdominal catheterization possible, thus avoiding removal of clothing or transfer to a toilet. Successfully addressing these limitations with a continent catheterizable channel can be an important element in establishing increased independence for patients.

A continent catheterizable channel has very high levels of continence, although it is associated with high rates of minor revisions and complications (16%–81%).[58-61] There is little evidence to support the superiority of one reconstruction type over another. A 2014, multi-institutional review of adult patients undergoing construction of a continent catheterizable channel compared two types of channels or procedures. In the 61-patient cohort, Redshaw *et al.* reported that patients with cutaneous ileal cecocystoplasty undergo fewer interventions to maintain a usable channel than patients with a tunneled continent catheterizable channel.[62] The study was limited, however, to a retrospective assessment of 61 nonrandomized patients. All reconstructive alternatives for continent diversion have associated complications, and surgeons caring for this population must tailor each reconstruction to the individual patient.[63]

Regardless of the type of reconstructive operation, the incidence of catheterization difficulties appears to be directly related to the following variables: type of continent stoma, experience of individual surgeon, patient habitus, and length of follow-up.[13,64] Most complications present within the first 5 years. However, lifelong evaluation is encouraged by most specialists caring for this population, as complications can present many years after the initial reconstruction.[59,65-68] Difficulty with catheterization can arise from underlying stomal stenosis (most common), false passages, tortuous channels, or other problems such as parastomal hernias or diverticula. Most often, these complications do not require surgical reconstruction, but can be managed with endoscopic or minor procedures.

The first step in evaluation will often include an attempt to place a catheter in an outpatient setting. This typically involves the placement of a well-lubricated catheter of the same or smaller size than what is routinely used by the patient. In order to empty the bladder properly, a urethral catheter can be placed—if the patient has urethral access. This is beneficial because a distended bladder may prevent catheterization of the channel by kinking the limb or by tightening the tunnel as it enters the bladder.[64] If placement in the outpatient setting is successful, an indwelling catheter can be left in place for 1 to 3 weeks.[65,66] At this step in evaluation, patient compliance with catheterization should be encouraged, as noncompliance is associated with higher rates of stomal stenosis.[58,66] Additionally,

a change in catheter type may be recommended by the provider at this time. If stomal stenosis develops, it can be addressed with dilation and a period of indwelling catheterization. Various authors have proposed a method of stenting (L-stent placement or a Malone antegrade continence enema [MACE] stopper), with a course of steroid ointment. The L-stent and the MACE stopper are intended to be used overnight or in between catheterizations. There are small published case series on the use of these devices to prevent the onset of stomal stenosis.[69,70] In addition to these devices, Welk *et al.* have described an outpatient trial of serial catheter dilation with indwelling catheterization for 2 to 3 weeks, followed by steroid ointment lubrication (0.1% betamethasone) for a period of 6 weeks.[59] The durability of steroid treatment has not been reported. Other authors have reported the successful implementation of triamcinolone injection for stomal stenosis, with success rates approaching those of formal revisions.[59,71] Endoscopic incision of a channel stricture has been described in the pediatric population, but no data currently exist for the adult population.

If catheter placement in an office/outpatient setting is not successful, either endoscopic or radiographic evaluation can be performed to further aid successful catheter placement, prior to formal surgical revision.

4.3.1.1 Endoscopic evaluation

Approximately 15% of patients with a catheterizable channel will require cystoscopic placement of a catheter after experiencing difficulties with catheterization.[65] Endoscopy of a catheterizable channel allows for direct visualization and identification of deeper complications. In various case series, early endoscopic management, in conjunction with dilation and wire-guided catheter placement, was associated with a reduced need for subsequent open channel revisions. Up to 22% of patients in these case series underwent more than one endoscopic intervention for catheterizable channel difficulties.[59,65,71]

The narrow lumen of a catheterizable channel typically requires that endoscopy is performed with a flexible or rigid pediatric cystoscope, a flexible hysteroscope, or a flexible adult ureteroscope. If endoscopy is not successful, a suprapubic tube—with either ultrasound-guided or open placement—may be necessary.

4.3.1.2 Radiographic evaluation

Fluoroscopic imaging or computed tomography can assist in the detection of trauma to a catheterizable channel, as well as in the evaluation of adjacent fluid collections, urinary extravasation, and foreign bodies (eg, calculi), which may result in difficulties with catheterization.[61,62,71] In centres with uroradiology expertise, fluoroscopic imaging of the catheterizable channel may allow safe wire-guided placement and catheterization in a radiology department or urology clinic.

In summary, there is no single correct way to catheterize a channel that has developed a problem with catheter placement. Guiding principles for selecting and using the most appropriate method should be based on knowing the options available and engaging experienced providers for catheter placement.

4.3.1.3 Surgical revision

The rates of surgical revision for stomal stenosis, or other catheterization problems, have been described mostly in the pediatric population. Pagliara *et al.* described retrospective outcomes of channel revision surgery in a 2018 multi-institutional cohort of 51 adult patients. Channel revisions were classified into three categories: suprafascial, subfascial, or total versus partial replacement. While channel revisions resulted in durable rates of channel patency and low incontinence rates, the procedures varied considerably; no single technique was identified as being more effective than another at providing durable patency while minimizing long-term complications.[71]

Most cases of suprafascial stenosis can be corrected by excising the scarred portion and advancing a local skin flap. Radojicic *et al.* also have described buccal mucosal grafting for the correction of stomal stenosis.[72]

If open channel revision is required, the affected segment of the channel is identified during a laparotomy. Depending on the length of the involved segment, the channel may be revised with either interposition of a bowel segment, marsupialization of the distal end, or complete replacement of the diseased channel with a new bowel segment and creation of a new continence mechanism. In cases where a new channel segment cannot be tunneled into the bladder, ileal channel cecocystoplasty versus intussusception ileal flap valve techniques have been described as alternative options, although long-term data on success are not available.[73]

4.3.1.4 Urethral catheter evaluation

Obesity is a long-recognized issue in patients with spinal dysraphism.[74-77] Along with reduced strength in upper limbs,[78] obesity may impact a patient's ongoing ability to catheterize. Both men and women can be affected by obesity—anecdotally, women may be more likely to be at risk. Obesity may also affect the safety or feasibility of reconstruction, thus limiting continent options to an indwelling catheter or urethral leakage. Long-term urethral catheters in men may be associated with a number of complications, including urethral strictures or cleavage, false passages, or inflation of a Foley balloon, which may further add to trouble performing CIC. Conversion to a suprapubic catheter may be necessary or, beyond that, a catheterizable stoma. It is important that patients and their caregivers are aware of the risks for complications, and, ideally, catheterization should be performed only by experienced practitioners or the patient him/herself.

4.3.1.4.1 Recommendation

- No high-grade evidence exists for the initial evaluation and management of catheterizable channels; expert opinion and case series data suggest that catheterization difficulty is common. There is some evidence for initial outpatient evaluation of the channel. If unsuccessful, this should be followed by an endoscopic attempt at wire-guided catheter placement. There is some evidence that prompt endoscopic evaluation may reduce rates for operative revision of the channel. Steroid injections, steroid ointments, and stenting between catheterizations may be safely used as adjunctive treatment, as suggested by lower-level evidence **[LOE 4-5; GOR C-D]**.

4.3.2 Catheterizable channel incontinence

Continence is achieved by several possible mechanisms, but the two most commonly used strategies are the flap valve and the nipple valve.[67] The flap valve principle was described by Paul Mitrofanoff and uses a continent appendicovesicostomy; this principle has been modified and implemented in various continent channel surgeries (detubularized ileum, colon, ureter, and fallopian tube). The nipple valve principle is used in ileal channel cecocystoplasty by reinforcing the ileocecal valve (as in the Kock pouch), which uses an intussuscepted ileocecal valve.

Reported rates of catheterizable channel incontinence range from 1% to 22%, with variability in the definition of stomal incontinence. In addition, the timing of incontinence can vary,[59] and may occur any time after the creation of a channel. Appropriate management is important because patients with persistent urinary incontinence after continent reconstruction experience a marked decrease in overall quality of life.[79]

When patients with AC and catheterizable channels present with incontinence, clinicians must evaluate the continence mechanism, as well as the reservoir. Acute incontinence through a stoma may be secondary to infrequent or incomplete emptying, UTIs, excessive mucus, or mucus impaction/stones. Once acute causes have been ruled out, additional study of the bladder and stoma can help to identify the underlying problem.

4.3.2.1 Endoscopic evaluation

Endoscopic examination of catheterizable channels can help identify saccular dilatation of the urinary tract that may allow pooling of urine or adversely affect the continence mechanism. In addition, endoscopy can allow clinicians to identify an intravesical channel that is too short to provide adequate continence, as might be the case in a mature-aged patient with an appendicovesicostomy. Further, acute factors, such as stone formation and excessive mucus, can be readily identified by endoscopy in an office/outpatient setting of the catheterizable channel and bladder.

4.3.2.2 Urodynamic evaluation

Because incontinence can be secondary to problems with the continence mechanism or the reservoir, or both, VUDS evaluation may help clinicians to accurately evaluate both filling and emptying of the bladder. Multichannel UDS can be performed to obtain intravesical, abdominal, and stomal pressure profilometry. However, there is no standardized value for what constitutes an abnormal reading in pressure profilometry of the catheterizable channel. The UDS catheter may also be placed through the urethra, if there is urethral access. After filling to a predetermined volume, stress manoeuvres, such as coughing, Valsalva, and Credé, can be performed to assess incontinence. In addition to assessing stress incontinence, cystometrograms can be used to assess storage compliance and the presence or absence of overactivity. In this way, UDS evaluation can help direct treatment.

4.3.2.3 Radiographic evaluation

Radiographic evaluation of the bladder and stoma is known as cystography. This can be performed independently or in conjunction with multichannel UDS. When available, clinicians may perform fluoroscopy at the time of UDS. Radiographic images can reveal whether there are abnormalities in the configuration of the augmented bladder that contribute to limitations in storage. In addition, in patients with incontinence secondary to impaired bladder compliance, fluoroscopic images can also help to visualize VUR. A finding of VUR necessitates appropriate treatment of compliance and storage prior to correction of incontinence.

4.3.3 Continence management

4.3.3.1 Increased catheterization frequency

A frequency-volume chart, used in conjunction with radiographic or UDS evaluation, can provide an effective way to prevent potentially high bladder volumes that increase the likelihood of incontinence.

4.3.3.2 Endoscopic injection of the continence mechanism

Injection of the continence mechanism with a bulking agent is a minimally invasive treatment, and studies on its implementation have reported low morbidity.[65,80,81] Different injection agents have been described in the literature, including bovine collagen, polydimethylsiloxane (PDMS), polytetrafluoroethylene, and dextranomer/hyaluronic acid copolymer (Dx/HA; Deflux®). An endoscopy is typically performed as an outpatient procedure, with the continence mechanism approached in a retrograde fashion. There are reports on injection at the distal stoma versus direct injection at the level of the continence mechanism, with submucosal injection of the catheterizable channel at the level of the continence mechanism being the most common approach. The injections are placed circumferentially until coaptation of the mucosa is achieved. Patients are typically able to resume intermittent catheterization immediately after completion of the procedure. There have been no direct comparisons between different bulking agents. Continence rates have been described by Roth *et al.* as between 50% (for early use of collagen) and 86% continence, and Riachy *et al.* reported a median follow-up of 72 months.[60,65,81,82]

At many centres, endoscopic injection is considered an alternative option prior to a formal revision procedure for patients with stomal incontinence. Centres have reported that formal open revision after injection of the catheterizable channel with the most commonly used injectable agents (ie, PDMS and Dx/HA) was not made more difficult than in patients who did not have injection. In cases of channel incontinence, some patients may benefit from having repeat injections; most patients who benefit become continent after receiving no more than two injections.[81] Durability of this treatment has proven variable, even though data are limited to small, single centre series with multiple, different bulking agents.[82-84]

4.3.3.3 Surgical channel revision

If expectant management or bulking agents fail to improve catheterizable channel continence, open surgical intervention may be necessary. Revision of an existing continence mechanism may be possible, otherwise, removal and replacement of the entire channel is likely to be necessary. Surgeons undertaking this work must have the skills to take on any surgical scenario, as it may only be possible to determine what will be necessary once surgery is underway.

4.3.3.3.1 Recommendation

- Incontinence is the most common risk for patients and may present any time after the creation of a catheterizable channel complication develops. Several retrospective case series support a stepwise approach, beginning with ambulatory endoscopic injection of a bulking agent, followed by formal revision, then channel replacement. Prior to any surgical revision, UDS evaluation of the reservoir should be undertaken to rule out concomitant problems with the pouch/bladder (eg, pouch contraction, high-pressure storage, stones, or other foreign object), which may be contributing to leakage **[LOE 4-5; GOR C-D]**.

4.4 Cancer Risk and Surveillance

4.4.1 Overview

As life expectancy increases for patients with neuropathic bladders, long-term outcomes have become increasingly important. Over the past two decades, a great deal of interest has been generated regarding the long-term risk for malignancy in patients with a congenital neuropathic bladder. Although it has long been known that patients with bladder exstrophy, or those managed with an indwelling catheter, were at high risk for aggressive cancer,[85-88] recent data have focused on patients who have undergone bladder reconstruction with intestinal segments.

4.4.2 Incidence

Indiana University published a series on three patients, in 2004, who all died from a malignancy that was related to intestinocystoplasty.[89] Other case reports and series have been published since, of which the vast majority concluded a high mortality rate after cancer detection. Subsequent publications have attempted to focus on defining the true incidence of malignancy in patients with congenital neuropathic bladder, identifying risk factors, evaluating efficacy of screening, and considering alternative treatment options.

Doug Husmann and co-workers have written extensively on the topic based on his large adult congenital referral practice[90,91] and a separate meta-analysis.[92] A 2009 literature review uncovered 20 cases of cancer in patients with a previous augmentation, giving a calculated incidence of 1.5% to 2.8%.[91] A 2017 review noted cancer was discovered at a median age of 41 years, a median of 14 years after augmentation.[92] Other data report a median age of 51 years and a median latency of 39 years.[93] Although the numbers were too small for definitive statistics, the risk appeared greater in those patients who were smokers, immunosuppressed after solid organ transplantation, or with bladder exstrophy. Rove's systematic review documented a 2% to 4 % incidence of bladder cancer in patients with a congenital anomaly, showing no difference between those with bladder augmentation or not.[92]

Presentation of these cancers is usually delayed and, accordingly, the outcome is very poor. In the SB population, Rove *et al.* published a systematic review that described a 1-year survival rate of 48% and a 2-year survival rate of 31% in patients with bladder cancer.[92] Survival was independent of augmentation status, with only 31% of the diagnoses occurring in patients with an intestinocystoplasty. The presence of an augmentation had a significantly higher rate of survival, and a median latency time from surgery to diagnosis of 14 years. Only 37% of all patients were followed regularly, which included ultrasound and cystoscopy; surveillance did not result in an improved rate of survival.

4.4.3 Surveillance

Because of the aggressive nature, poor outcomes, and late presentation of bladder cancer, several groups have examined screening programs. The lack of efficacy in screening was first presented by Higuchi *et al.*, showing that 5 years of regular cytology and cystoscopy in 65 patients with an enterocystoplasty failed to reveal any malignancies.[94] Hamid *et al.* performed a prospective study in

92 consecutive patients, with cystoscopy added to their regular, annual clinic visits. After a median follow-up of 15 years, no cancer was detected, although one patient presented with a malignancy despite normal surveillance cystoscopy.[95] Therefore, no group has been able to recommend routine surveillance cystoscopy; however, all groups agree that regular follow-up is important, and that worrisome symptoms or concerning radiological findings (eg, hematuria, recurrent UTIs, suprapubic pain, bladder filling defect/mass) warrant endoscopic investigation.

4.4.4 Risk factors

The type of intestinal segment used for bladder augmentation is often considered a risk factor for cancer, with many a gastric segment posing the most-high risk. Although multiple case reports exist, the largest series is from Castellan *et al.*, who in 2012 reported a 10% mortality rate from malignancy in gastric segments.[96]

However, the systematic review by Rove *et al.* in 2017 was not able to demonstrate an increased risk among gastric, colonic, or ileal segments.[92] There is even a case report of fatal malignancy in an auto-augmented bladder (no additional tissue was transferred into the bladder), reinforcing the notion that degeneration is likely due to conditions inherent in a neuropathic bladder itself or other factors, such as chronic inflammation and bacteriuria, but not solely due to the presence of a bowel segment.

Overall mortality, from all causes, after a bladder augmentation in childhood was reported by Szymanski *et al.* at 7.6%, with deaths occurring at a median of 10.6 years after augmentation.[97] Mortality was secondary to infection (including infected ventriculoperitoneal shunts) at 56%, but no patient in this cohort died from malignancy. Husmann reviewed 385 patients at his transitional clinic and reported five deaths, from bladder rupture (1) and renal failure (4), compared with six patients who succumbed to malignancy arising in the bladder.[93] Obesity and cognitive status were felt to be major risk factors for all causes of mortality.

Although data are scarce, they are evolving and seem to be consistent with the hypothesis that the risk of mortality from malignancy is higher in patients who underwent intestinocystoplasty than in the general population. The etiology of increased lethality from bladder cancer is not clear, but may be due to chronic inflammation or infection. Furthermore, beyond regular follow-up, screening mechanisms have not been successful at improving diagnosis or decreasing mortality.

4.4.4.1 Recommendations

- There are sufficient data to conclude that pediatric patients with neuropathic bladders are at an increased risk for developing carcinoma of the bladder in adulthood, although lethality of bladder cancers encountered in this population appears to be higher than in the general population **[LOE 3]**.

- There may be an increased risk for cancer after a gastric cystoplasty **[LOE 4]**.

- However, intensive screening protocols have not been effective at decreasing mortality **[LOE 4]**; therefore, it is recommended that these patients be followed with an annual ultrasound and clinical assessment, with great care taken to investigate hematuria, recurrent UTIs, changes in clinical status, or new radiographic findings **[LOE 4]**.

4.5 Summary of Recommendations

4.2.4.1 Recommendation for inappropriate treatment of asymptomatic bacteriuria

- Routine screening for bacteriuria in the absence of symptoms should not be undertaken. Exceptions to this include patients who will undergo invasive procedure, or endoscopic or open surgery of the urinary tract—these patients should have a urine culture taken prior to any procedure, given the high likelihood of bacteriuria **[LOE 1; GOR A-B]**.

4.2.5.1 Recommendation for diagnosis of acute UTIs

- A urine culture should be obtained to allow antibiotic treatment to be tailored for symptomatic UTIs in patients with NGB **[LOE 3; GOR C]**.

4.2.6.3.1 Recommendation for invasive testing

- Endoscopic evaluation and urodynamic testing should be considered in adult patients with congenital NGB who have new or recurrent symptomatic UTIs **[LOE 5; GOR C-D]**.

4.2.7.3.1 Recommendations for prophylactic oral medications

- Routine antibiotic prophylaxis is not recommended due to its low efficacy in preventing symptomatic infections and risk for antibiotic resistance **[LOE 2; GOR B]**.

- Methenamine salts have not been found effective in the NGB population; therefore, they are not recommended **[LOE 2; GOR C]**.

4.2.7.4.1 Recommendation for intravesical irrigation and medications

- Intravesical irrigation with at least 240 mL of saline irrigation, or intravesical instillations with gentamicin, can be used on a short-term basis in patients with NGB for symptomatic UTI prevention, though other agents cannot be recommended **[LOE 4; GOR C-D]**.

4.2.7.6.1 Recommendation for other oral supplements

- There is no evidence to support the use of cranberry derivatives or D-mannose in the adult NGB population **[LOE 1; GOR A-B]**.

4.3.1.4.1 Recommendation for urethral catheter evaluation

- No high-grade evidence exists for the initial evaluation and management of catheterizable channels; expert opinion and case series data suggest that catheterization difficulty is common. There is some evidence for initial outpatient evaluation of the channel. If unsuccessful, this should be followed by an endoscopic attempt at wire-guided catheter placement. There is some evidence that prompt endoscopic evaluation may reduce rates for operative revision of the channel. Steroid injections, steroid ointments, and stenting between catheterizations may be safely used as adjunctive treatment, as suggested by lower-level evidence **[LOE 4-5; GOR C-D]**.

4.3.3.3.1 Recommendation for surgical channel revision

- Incontinence is the most common risk for patients and may present any time after the creation of a catheterizable channel complication develops. Several retrospective case series support a stepwise approach, beginning with ambulatory endoscopic injection of a bulking agent, followed by formal revision, then channel replacement. Prior to any surgical revision, UDS evaluation of the reservoir should be undertaken to rule out concomitant problems with the pouch/bladder (eg, pouch contraction, high-pressure storage, stones, or other foreign object), which may be contributing to leakage **[LOE 4-5; GOR C-D]**.

4.4.4.1 Recommendations for cancer risk and surveillance

- There are sufficient data to conclude that pediatric patients with neuropathic bladders are at an increased risk for developing carcinoma of the bladder in adulthood, although lethality of bladder cancers encountered in this population appears to be higher than in the general population **[LOE 3]**.

- There may be an increased risk for cancer after a gastric cystoplasty **[LOE 4]**.

- However, intensive screening protocols have not been effective at decreasing mortality **[LOE 4]**; therefore, it is recommended that these patients be followed with an annual ultrasound and clinical assessment, with great care taken to investigate hematuria, recurrent UTIs, changes in clinical status, or new radiographic findings **[LOE 4]**.

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C5

Upper Tract Considerations

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Upper Tract Considerations

5.1 Introduction

One of the first priorities for any urologist is the preservation of a patient's renal function. The kidneys may be injured perinatally or during childhood by insults and comorbidities such as critical illness, infection, trauma, or diabetes mellitus. Infants born with congenital anomalies of the kidney and urinary tract (CAKUT) are at risk for chronic kidney disease (CKD). Others have significant genitourinary anomalies that may be associated with renal anomalies or with bladder dysfunction that places the kidneys at increased risk of damage.

For affected newborns, perinatal predictors of future CKD, such as oligohydramnios, bilateral urinary tract dilation, and serum creatinine nadir, may provide valuable information for families and prompt the need for lifelong follow-up with nephrology and/or urology.[1]

Multidisciplinary care is important to manage the bladder and the kidneys in individuals with cloacal exstrophy, neuropathic bladder dysfunction, cloacal anomalies, and other similarly complex conditions. Teenagers and young adults are notorious for challenging the importance of prescribed self-care; there may also be age- and gender-based changes in the urinary tract. These points underscore the importance of early consultation and lifelong follow-up in these patients.

5.2 Nephrologic Surveillance and Considerations to Preserve Function

5.2.1 Challenges in renal function measurement

Managing renal function in children and adults with complex congenital urologic conditions is a critical component of managing overall health. However, measurement of renal function can be challenging for a variety of reasons, including:

- Changing renal function with age (particularly around puberty)
- Use of renal function equations not validated in this patient population
- Limitations of imaging modalities for accurate assessment of renal injury

In this section, the basic function of the kidneys is reviewed, as well as outcomes of renal injury and specific challenges of measuring renal function in individuals with complex congenital urologic conditions.

The role of the kidneys includes removal of waste, toxins, and excess fluid from the bloodstream whilst regulating blood pressure, red blood cell production, bone health, and electrolytes to achieve homeostasis. Renal function can be measured by glomerular filtration rate (GFR), which estimates volume of blood that passes through the glomeruli each minute. While the number of glomeruli is fixed at birth, several innate compensatory mechanisms allow maintenance of a near-constant GFR. Reduction in the number of glomeruli or disruption of these compensatory mechanisms decreases GFR and can cause CKD, which in turn can lead to adverse downstream outcomes. Several challenges exist for measuring kidney function accurately in patients with complex congenital urologic conditions.

GFR steadily increases after birth due to maturation of the kidney and somatic growth, reaching adult levels at around 2 years. During infancy and early childhood, as the kidneys continue to mature, renal function may be particularly vulnerable to chronic infections or acute kidney injury (AKI). Once through puberty, when somatic growth slows, renal function tends to stabilize. In individuals with complex congenital urologic conditions, renal dysplasia or hypoplasia may affect the trajectory of both renal and somatic growth and subsequently reduce the ultimate potential adult renal function. CAKUT has been associated with worse renal outcomes.[2,3] Thus, it is important to understand the expected normal GFR related to age, as this may be impaired with CAKUT (**Table 5-1**).

TABLE 5–1 Normal GFR in Children and Adolescents[4]

Age (Sex)	Mean GFR ± SD (mL/min/1.73 m²)
1 wk (males and females)	41 ± 15
2–8 wk (males and females)	66 ± 25
>8 wk (males and females)	96 ± 22
2–12 y (males and females)	133 ± 27
13–21 y (males)	140 ± 30
13–21 y (females)	126 ± 22

SD indicates standard deviation.

Abbreviation: GFR: glomerular filtration rate.

In addition, measurement of true GFR is neither easy nor cheap. Plasma clearance tests, which are considered the gold standard for measuring true GFR, require multiple blood samples and a protocol that is several hours long.[5] Urinary creatinine clearance is a close approximation of GFR, but requires a long collection period of 6 to 24 hours and is prone to errors in collection and timing.[5] Serum creatinine levels correlate with GFR, but creatinine is secreted by proximal tubular cells within the nephron and varies with muscle mass.[5] Renal function is frequently approximated using equations to calculate estimated GFR (eGFR). These equations rely on demographic data, such as gender and race; laboratory data, such as serum creatinine; and, for children, anthropometric data, such as height, to generate the eGFR value (**Table 5-2**).

TABLE 5–2 Validated eGFR estimating equations for children (1-18 years old) and adults (>18 years old).

Population	Equation name	Equation for eGFR (mL/min/1.73m²)
Children	"bedside" Schwartz creatinine[6]	0.413 • (height/Cr)
	Schwartz Cystatin-C[7]	$70.69 \bullet (CysC^{-0.931})$
	CKiD-creatinine-Cystatin-C[7]	If male: $39.8 \bullet (height/(100 \bullet Cr))^{0.456} \bullet (1.8/CysC)^{0.418} \bullet (30/BUN)^{0.079} \bullet 1.076 \bullet (height/(100 \bullet 1.4))^{0.179}$ If female: $39.8 \bullet (height/(100 \bullet Cr))^{0.456} \bullet (1.8/CysC)^{0.418} \bullet (30/BUN)^{0.079} \bullet (height/(100 \bullet 1.4))^{0.179}$
Adults	CKD-EPI-creatinine[8]	If **non-black male**: $141 \bullet \min(Cr/0.9,1)^{-0.411} \bullet \max(Cr/0.9,1)^{-1.209} \bullet 0.993^{age}$ If **black male**: $141 \bullet \min(Cr/0.9,1)^{-0.411} \bullet \max(Cr/0.9,1)^{-1.209} \bullet 0.993^{age} \bullet 1.159$ If **non-black female**: $141 \bullet \min(Cr/0.7,1)^{-0.329} \bullet \max(Cr/0.7,1)^{-1.209} \bullet 0.993^{age} \bullet 1.018$ If **black female**: $141 \bullet \min(Cr/0.7,1)^{-0.329} \bullet \max(Cr/0.7,1)^{-1.209} \bullet 0.993^{age} \bullet 1.018 \bullet 1.159$
	CKD-EPI-Cystatin-C[9]	If **male**: $133 \bullet \min(CysC/0.8,1)^{-0.499} \bullet \max(CysC/0.8,1)^{-1.328} \bullet 0.996^{age}$ If **female**: $133 \bullet \min(CysC/0.8,1)^{-0.499} \bullet \max(CysC/0.8,1)^{-1.328} \bullet 0.996^{age} \bullet 0.932$
	CKD-EPI-creatinine-Cystatin-C[9]	If **non-black male**: $135 \bullet \min(Cr/0.9,1)^{-0.207} \bullet \max(Cr/0.9,1)^{-0.601} \bullet \min(CysC/0.8,1)^{-0.375} \bullet \max(CysC/0.8,1)^{-0.711} \bullet 0.995^{age}$ If **black male**: $135 \bullet \min(Cr/0.9,1)^{-0.207} \bullet \max(Cr/0.9,1)^{-0.601} \bullet \min(CysC/0.8,1)^{-0.375} \bullet \max(CysC/0.8,1)^{-0.711} \bullet 0.995^{age} \bullet 1.08$ If **non-black female**: $135 \bullet \min(Cr/0.7,1)^{-0.248} \bullet \max(Cr/0.7,1)^{-0.601} \bullet \min(CysC/0.8,1)^{-0.375} \bullet \max(CysC/0.8,1)^{-0.711} \bullet 0.995^{age} \bullet 0.969$ If **black female**: $135 \bullet \min(Cr/0.7,1)^{-0.248} \bullet \max(Cr/0.7,1)^{-0.601} \bullet \min(CysC/0.8,1)^{-0.375} \bullet \max(CysC/0.8,1)^{-0.711} \bullet 0.995^{age} \bullet 0.969 \bullet 1.08$

Abbreviations: BUN: blood urea nitrogen; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CKD-EPI-Cr: Chronic Kidney Disease Epidemiology Collaboration creatinine; CKD-EPI-CysC: Chronic Kidney Disease Epidemiology Collaboration cystatin C; CKiD: Chronic Kidney Disease in Children study; Cr: creatinine; CysC: cystatin C; eGFR: estimated glomerular filtration rate; max: maximum; min: minimum.

To date, several eGFR equations have been derived and validated for children ages 1 to 18 years old,[6,7] and in adults ages 18 years old and over,[8,9] using plasma clearance tests as the gold standard comparator. However, the study cohorts used to generate these equations excluded individuals with complex urologic conditions. Using spina bifida as an example, patients with this condition often have shorter stature and less muscle mass than age-matched controls, leading to inaccurate height and serum creatinine values, respectively, and thereby inaccurate eGFR values.[10,11] Thus, although the same eGFR equations are used, they have not been well validated against gold-standard plasma clearance tests in these complex patients.

Other tests for measuring renal function face their own unique challenges in individuals with complex congenital urologic conditions. Imaging studies such as renal ultrasound or nuclear medicine renal scans can detect radiographic signs of renal injury, such as hydronephrosis or renal scarring. However, patients with congenital urologic conditions may have abnormal body habitus, including contractures or obesity, which make ultrasound studies technically difficult. In children who suffer recurrent urinary tract infections (UTIs), repeat imaging with ionizing radiation, eg, nuclear scans, is a concern due to the increased risk of secondary malignancies.[12,13] Although other blood tests, such as serum cystatin C, appear to be more accurate for renal function than serum creatinine,[14] they are not commonly available or used in clinical practice. Further research into newer, more accurate, and validated measures of renal function may help with the prediction, diagnosis and management of CKD.

5.2.2 Standard surveillance to optimize longevity of native kidneys

Collaboration between urologists and nephrologists is key for lifelong renal protection. Urologists tend to adopt a more anatomical approach and have longer-term focus on lower urinary tract (LUT) function. The nephrologist's focus is on markers of upper tract damage, such as renal function, proteinuria, and hypertension, as well as avenues for renoprotection. Furthermore, the nephrologist has expertise in the medical management of CKD and associated metabolic abnormalities. Studies have shown that early involvement of a nephrologist in a patient with CKD reduces mortality and hospitalization.[15]

Imaging is an important component of surveillance. Urinary tract ultrasound imaging is a safe, simple, and relatively inexpensive tool.[16] Ultrasound is useful to diagnose and follow up on:

- Renal growth, including compensatory hypertrophy
- Renal scarring
- Hydronephrosis
- Involution of multicystic dysplastic kidney
- Upper tract changes as surrogate for bladder changes or vesicoureteral reflux (VUR) in neurogenic bladder
- Renal and bladder calculi

A dynamic renal scan may be indicated for worsening hydronephrosis to better assess for changes in differential function or obstruction.[16] Technetium-99m-dimercaptosuccinic acid (DMSA) renal scan, where available, may be a better assessment of renal scarring compared to ultrasound. For those with VUR, obstructive uropathy, or neurogenic bladder, with or without recurrent febrile UTI, DMSA may be helpful to assess for renal cortical defects and differential function.[17]

Studies such as urodynamic assessment, cystogram, dynamic renal scans for obstruction, or magnetic resonance urography are often performed at the discretion of the urologist based on clinical changes or new, concerning ultrasound changes.[16]

Guidelines have been developed for evaluation and management of CKD.[18-19] Markers of CKD in patients with congenital abnormalities of the urinary tract include albuminuria, electrolyte abnormalities or other evidence of renal tubular dysfunction, or structural abnormalities detected by imaging. CKD is classified into categories based on GFR (**Table 5-3**).[18]

TABLE 5–3 Classification of Stages of CKD

CKD Stage	GFR (mL/min/1.73 m^2)
I	≥90
II	60–89
III	30–59
IV	15–29
V	<15 (or dialysis)

Abbreviations: CKD: chronic kidney disease; GFR: glomerular filtration rate.

Sources: *Levin A, Stevens PE, Bilous RW, et al. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1–150.*

Hogg R, Furth S, Lemley K, et al. National Kidney Disease Foundation's Kidney disease outcomes quality initiative clinical practice guideline for chronic kidney disease in children and adolescents. Pediatrics. 2003;111(6 Pt 1):1416–1421.

Patients with CKD are at risk for hypertension, proteinuria, secondary hyperparathyroidism, anemia and other metabolic derangements. In pediatrics, children with CKD also develop growth hormone resistance and require growth hormone to optimize their adult height.[20]

GFR should be assessed in all patients and CKD classification documented. Normal GFR in young adults is approximately 125 mL/minute/1.73 m^2. Normal GFR in pediatrics varies by age and increases significantly in the first year of life.[4] Creatinine and a GFR estimating equation (in children: modified Schwartz formula; in adults: Modification of Diet in Renal Disease study (MDRD) equation or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine 2009 equation, or Cockcroft-Gault creatinine equation) are recommended for initial assessment. These are reviewed in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[18] In some patients, particularly those with reduced muscle mass, additional tests may be required when the eGFR using serum creatinine is not validated. In such cases, cystatin C may be measured, and the 2012 CKD-EPI cystatin C (CKD-EPI-CysC) and 2012 CKD-EPI creatinine–cystatin C equations can be used. These are also reviewed extensively in the KDIGO guidelines.[18] Lastly, GFR can be measured using creatinine clearance or exogenous filtration markers (inulin, iothalamate, iohexol, ethylenediaminetetraacetic acid [EDTA], or diethylenetriaminepentaacetic acid [DTPA]).[18]

Frequency of measurement of renal function is at the discretion of the nephrologist, depending on the rate of change and other risk factors. Stable patients may have laboratory studies annually, whereas patients with increased acute risks for progression may require quite frequent monitoring.

Proteinuria is a useful marker of renal damage, and monitoring for albuminuria/proteinuria should occur at least annually with quantification of albumin-to-creatinine ratio and protein-to-creatinine ratio on a first morning urine. Higher albuminuria is associated with increased risk of higher grades of CKD and an increased rate of progression.[21,22] Amelioration of proteinuria also has been associated with delayed progression of CKD. The utility of renin-angiotensin system antagonists to reduce proteinuria is discussed in the Renoprotective Measures section (5.1.3) of this chapter.

Hypertension is also associated with renal scarring and CKD, and increases the risk for CKD progression.[23,24] Blood pressure should be measured manually at all physician visits, at least annually. It may also be useful to monitor 24-hour ambulatory blood pressure and to use an echocardiogram to assess for left ventricular hypertrophy. Proactive treatment of hypertension may also delay CKD progression. Dietary salt restriction (<2 g/day) is also important for optimal blood pressure control.

Patients with CKD are at increased risk of AKI, and thus monitoring during intercurrent illness and during procedures that may require contrast (computed tomography [CT] scan or angiography) is important.[18]

In the pediatric population, obstructive uropathy and especially renal dysplasia are associated with salt-wasting and urinary-concentrating abnormalities. Monitoring for polyuria and then implementing increased free-water intake as well as sodium supplements, when indicated, is important for prevention of volume depletion and AKI, as well as for normal growth.[25]

Electrolytes and acid-base status monitoring are important, as they can impact bone health and growth. If the serum bicarbonate is consistently less than 22 mmol/L, treatment with oral bicarbonate supplementation is indicated. Correction of acidosis may also reduce progression of CKD. Serum potassium also should be monitored.[25,26]

Parathyroid hormone, calcium, phosphate, and 25-hydroxyvitamin D should be assessed at least annually, and appropriate measures instituted for hyperphosphatemia, vitamin D deficiency, hypocalcemia, or hyperparathyroidism. CKD patients should seek the advice of a renal dietician to review metabolic abnormalities and provide advice on intake/restriction of salt, phosphate, and potassium.[25,27]

Patients with CKD are at risk for anemia. Hemoglobin and/or hematocrit should be monitored for screening, and further testing may be warranted thereafter. Guidelines exist for initiation of erythropoietin therapy, as well as for hemoglobin targets.[28]

All CKD patients should remain up to date with vaccinations, and guidelines exist on pneumococcal vaccine and hepatitis B vaccine use.[18]

5.2.3 Renoprotective measures

Beyond surveillance and intervention to protect general health in the setting of CKD, there are several measures to protect and preserve the kidneys. In patients with CKD, nephrotoxins should be avoided. The list of agents to avoid includes non-steroidal anti-inflammatory agents, and this important counselling should start in infancy. GFR should be taken into consideration for any drug dosing.

Some concurrent medications may need to be reduced or temporarily withheld during intercurrent illness due to risk of AKI, including: angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics, metformin, lithium, and digoxin.

The risks and benefits of contrast agents should be assessed in all CKD patients with GFR <60 mL/minute/1.73 m^2 and discussed with the patient, radiologist and nephrologist. Hydration protocols before, during, and after the procedure should be used and renal function should be monitored for 2 to 3 days postprocedure. Gadolinium should not be used in a patient with a GFR <30 mL/minute/1.73 m^2.[18,29]

For patients with proteinuria and progressive renal failure, blockade of the renin-angiotensin system with ACEIs or ARBs are preferred renoprotective interventions. Use of an ACEI or ARB to reduce proteinuria was initially studied in those with diabetic nephropathy and found to delay progression of CKD; it has since been applied to both glomerular and nonglomerular causes.[30,31]

ACEI therapy has been shown to slow the decline in GFR and to reduce proteinuria in individuals with urologic anomalies. Initiation of renin-angiotensin system antagonists is recommended for increasing proteinuria or for proteinuria exceeding 50 mg/mmol (0.5 g/day). In order to impact the trajectory of decline in eGFR, the window of opportunity for beginning these medications appears to be in the 40 to 50 mL/minute range.[32]

Section 5.2 of this chapter illustrates the concerning impact of proteinuria in progressive deterioration to ESRD. Proteinuria should be assessed using early-morning spot albumin-creatinine ratio. When indicated, ACEI should be started at a low dose and increased to a maximum tolerated dose, aiming for target blood pressure of less than 130/80. Electrolytes should be checked 2 weeks after starting ACEI and after every incremental increase.

5.2.4 Future directions, novel markers, and new tools beyond creatinine

The most common serum biomarker for estimation of GFR is creatinine. Equations to estimate GFR are useful tools as part of routine CKD clinical care.[33] Many creatinine equations are useful for the bedside or point-of-care estimation of GFR, such as the modified Schwartz formula, MDRD, or CKD-EPI equations. Creatinine-based GFR estimates may not be as accurate due to tubular secretion of creatinine and the relationship with muscle mass. There are patient populations where creatinine-based GFR equations are not as reliable, such as in patients with spina bifida who have low muscle mass or those with enterocystoplasty. In patients with spina bifida or other populations where it is difficult to measure height, calculation of GFR based on height or body surface area may also be difficult.

Cystatin C is an endogenous proteinase inhibitor produced at a constant rate in the body and is freely filtered by the glomerulus.[34] It is reabsorbed and catabolized nearly completely by renal proximal tubular cells, and so it is not significantly excreted in the urine. Therefore, cystatin C cannot be used to calculate a *clearance* GFR.

Cystatin-based estimated GFR equations have been developed.[35] Variability of cystatin C between individuals is less than creatinine and it does not seem to be influenced by muscle mass, gender, or age after 1 year. Limitations include:

- Potential underestimation in renal transplant
- Potential influence of smoking status and C-reactive protein on concentration
- Presence of cystatin C in the urine during glomerular and tubular injury

Other methods of measuring clearance include use of inulin, which is freely filtered and not reabsorbed, secreted, or metabolized by the kidney.[34] However, inulin clearance is technically difficult and requires an indwelling catheter, and inulin may not be readily available. These factors limit inulin's practicality as a widespread assessment of renal function.

Several radionuclide components are available for single injection clearance measurement.[34] These include iothalamate, DTPA, and EDTA. Each agent has some limitations, but plasma clearance of DTPA and EDTA correlate well with inulin clearance.[34] Iohexol plasma disappearance as measurement of GFR in children has extensively been validated in the CKiD studies as accurate and reliable.[36]

There has been significant interest in urinary biomarkers. Many tubular and glomerular proteins are impacted by injury secondary to obstruction, renal vasoconstriction, hypoxia, and ischemia.[37,38] Biomarkers of fibrosis and tubulointerstitial injury may be useful in the future as markers of CKD and its progression. Currently, no biomarkers are approved by the US Food and Drug Administration for clinical use, and research is needed both in pediatrics and adults.

Urinary proteomic studies in patients with obstructive uropathy have shown varying results. In some infants with Society for Fetal Urology (SFU) grade 4 ureteropelvic junction (UPJ) obstruction, the urine proteome differed from age-matched controls and included proteins involved in inflammatory response, apoptosis, tubular injury and fibrosis, and oxidative stress.[39] It is possible that future discovery of urinary biomarkers may provide another tool to assist the urologist in consideration of observation versus intervention for urinary obstruction.

Kidney failure risk equations (KFREs) are a newer tool developed to help clinicians identify patients at high risk for CKD progression and have been useful for implementation of interventions to slow CKD progression, as well as for planning the timing of dialysis access placement or renal transplantation.[40,41] These equations are designed for patients with CKD stages III to V (GFR 10–59 mL/min/1.73 m^2).

The KFRE use either a four-variable equation (age, sex, eGFR, and ratio of albumin to creatinine) or an eight-variable equation (the four variables mentioned above plus serum calcium, phosphate, bicarbonate, and albumin levels). These risk factor equations accurately predict the 2- and 5-year probability of kidney failure in CKD, with increased precision by the eight-variable equation. Younger

age, male sex, lower eGFR, and higher albuminuria are associated with a higher risk of kidney failure defined by initiation of dialysis or transplantation. This study was initially validated in North America, and then a regional calibration factor was added in other cohorts.

More recently, this formula was assessed in the Chronic Kidney Disease in Children study (CKiD).[42] In children with CKD stage III to V, the KFRE tool provided equally accurate information about progression to ESRD. In addition, the CKiD study of the KFRE tool found that it performed better in younger children. They speculated that there was a higher incidence of CAKUT in these children, and that the pattern of progression might be more predictable. In children, there was also better performance of the equation in those with Hispanic ethnicity; this needs to be explored further. As with its use in adults, the CKiD authors suggested that KFRE could be a tool to determine the timing of ESRD onset and to better plan for living donor work-up and for pre-emptive renal transplant in children.

5.2.5 When should urologists consult nephrologists?

Increasingly, the care recommended for many urologic conditions, such as VUR, has moved away from immediate operative management to more expectant and medical management. Optimal renal function management of many complex congenital urologic conditions thereby relies on a successful, multidisciplinary relationship between urology and nephrology. As outlined below, urologists should consult nephrologists in several specific clinical scenarios.

Development of or deterioration in CKD, as measured by eGFR, warrants a referral to nephrology. Classically, CKD stage III or worse (eg, eGFR <60 mL/min/1.73 m^2) should prompt a nephrology consultation.[43] However, any worrisome clinical scenario, such as neurogenic bladder with suspicion for upper tract change related to pressure or reflux, even at a less severe CKD stage, should be considered for nephrology referral. There would be lower threshold for referral of congenital solitary kidneys to nephrology, even if CKD by eGFR measurement has not developed. Congenital solitary kidney belongs to the umbrella group CAKUT, which constitutes most causes of CKD in children.[44,45]

CAKUT encompasses various pathological conditions, including posterior urethral valves (PUVs), VUR, solitary kidney, renal dysplasia or hypoplasia, multicystic dysplastic kidney, and genetic cystic diseases. Recent evidence suggests a significant association between CAKUT and ESRD.

A population-based cohort study of >1 million Israeli adolescents found a significant association between history of CAKUT and development of ESRD (adjusted hazard ratio [HR] 5.19, 95% confidence interval [CI]: 3.41–7.90).[3] Within CAKUT, having a congenital solitary kidney is significantly associated with higher risk for dialysis (adjusted HR 2.43, 95% CI: 1.09–5.40) compared to having certain other CAKUT entities, including renal dysplasia or multicystic dysplastic kidney.[2] Other severe forms of CAKUT with known natural history of progression to ESRD, such as PUVs or polycystic kidney disease, should also be referred to nephrology for evaluation, serial surveillance, and medical management. Essentially, the threshold to discuss or refer a patient with CAKUT to nephrology should remain low.

A certain subset of patients will develop hypertension or proteinuria without manifesting CKD by eGFR measurement. These individuals may not have had CAKUT but may have other risk factors for poor renal outcomes. Two examples are hereditary glomerulopathies and nephritic syndromes, which may manifest initially as hematuria or hypertension that is incidentally detected on a routine office measurement. While discussion of the nuances and management of glomerular causes of childhood CKD are beyond the scope of this chapter, persistent gross or microhematuria after exclusion of infection warrants evaluation by nephrology. The primary concern is that the decline in kidney function over time appears to be faster among children with glomerular causes of CKD when compared with nonglomerular causes.[46] While optimal management of this patient subpopulation sits with nephrology rather than urology, the urologist should be cognizant of family histories of kidney disease or hypertension and make referrals where appropriate.

A final subset of patients who benefit from joint uro-nephrologic care are those with kidney stones. While 25% to 50% of stones with acute colic episodes require surgical intervention by urology,[47] nephrolithiasis is estimated to recur in 50% of children at a median of 3 years.[48] Primary prevention of recurrent stone disease is paramount and, at least in the pediatric population, is often managed by the pediatric nephrology team. Metabolic evaluation can reveal the etiology behind stone formation, such as hypercalciuria or hypocitraturia,[49] for which effective medical interventions exist. Even more basic medical management strategies such as modifications of diet and fluid intake can be effective in reducing stone recurrence.[50] Ideally, joint multidisciplinary clinics combining both urology and nephrology are a forum to assess and treat recurrent stone-formers.

In summary, urologists will frequently encounter patients who have not been, but should be, evaluated by nephrology. Beyond an eGFR-based diagnosis of CKD, underlying conditions such as severe CAKUT phenotypes (eg, solitary kidney, PUVs, polycystic kidney disease), concern for intrinsic renal disease (eg, nephrotic or nephritic syndromes), and nephrolithiasis should be referred to nephrology.

5.3 Progressive Renal Deterioration

5.3.1 Expected rate of renal deterioration in setting of congenital uropathies and changes in adolescence

CAKUT accounts for the greatest proportion of cases of CKD in children as described in the data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS).[51] Several studies have looked at progression in the CAKUT population. This is important, as there are multiple known modifiable risk factors that could significantly shorten the time to ESRD (eg, proteinuria and hypertension).

In the CKiD study of children with CKD of nonglomerular origin, which includes CAKUT, higher baseline proteinuria and systolic blood pressure were independently associated with CKD progression.[52] Further evaluation of the CKiD nonglomerular disease cohort demonstrated that lower baseline GFR, dyslipidemia at baseline, higher grade proteinuria, hyperphosphatemia, acidosis, hypertension, anemia, and hypoalbuminemia were predictors of more rapid disease progression. Correction of some of these risk factors may delay progression of CKD and is the basis for ongoing interventional trials.

A large Italian cohort of children with CAKUT followed for up to 30 years looked for diagnostic variables that impacted poor renal outcome.[53] Higher creatinine, proteinuria, and presence of VUR were all associated with higher risk of progression in all types of CAKUT. Poorer outcome was noted for bilateral renal hypodysplasia, solitary kidney, and PUVs compared to other categories of CAKUT. The risk in solitary kidney was unexpected, as prior literature shows a small incidence of CKD in those with solitary kidney, with a known risk of hypertension and proteinuria due to hyperfiltration. The authors suggested that subclinical defects of the solitary kidney might account for poor prognosis in this group. Hence, as in all patients with CAKUT, annual screening of blood pressure and a urine dipstick for proteinuria are indicated, as well as periodic renal function assessment.

One single-centre study evaluated risk factors for progression in children with renal dysplasia, reflux nephropathy, or renal obstruction.[54] In the first 5 years of life, 82% of children showed early improvement in renal function lasting until a median age of 3.2 years. In over half, from ages 3.2 to 11.4 years, renal function remained stable, whereas deterioration was noted in 48%. Around puberty, 43% had deterioration, but 57% continued to have stable function. Risk factors for rapid deterioration included higher proteinuria, more than two febrile UTIs, hypertension, and eGFR at onset of less than 40 mL/minute/1.73 m^2.

There are very few studies assessing the impact of puberty on CKD, despite the observation that many young people demonstrate renal deterioration during periadolescence. NAPRTCS registry data show an increased number of adolescents on dialysis compared to other age groups.[55] The Italian Pediatric Registry of Renal Failure (ItalKid) Project reported a sharp decline in renal function during puberty and early post puberty.[56] The ItalKid Project reported data on 935 patients with renal hypodysplasia

between 1990 and 2002. Estimated probability of ESRD was 9.4% at age 10 and 51.8% by age 18. The break point occurred earlier in females than in males and corresponded with the onset of puberty in both.[57]

No studies have investigated specific risk factors during puberty that may impact progression. The underlying pathophysiology of puberty impacting renal disease is not known. ItalKid authors hypothesized that progression during adolescence may depend on the impact of sex hormones, as well as the imbalance between residual renal mass and rapid growth.[57] In animal models, both castration and oophorectomy have been shown to reduce proteinuria and glomerulosclerosis in unilaterally nephrectomized rats.[58,59] Certainly, there has been much interest in differences in renal progression between males and females.

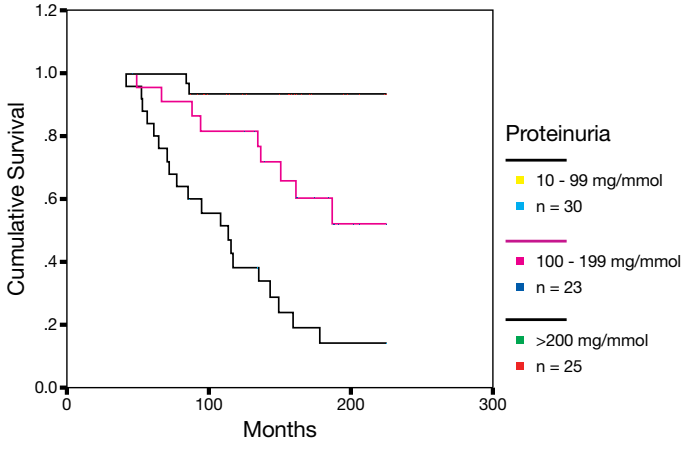
Estradiol has been thought of as a protective factor and testosterone as potentially detrimental. Mesangial cells have estrogen receptors. Male and female kidneys may have different quantities of androgen and estrogen receptors, and therefore changes in response to renal injury may be gender dependent.[60] Podocytes also have testosterone and estrogen receptors with opposing effects.[61] Testosterone causes podocyte apoptosis. Estradiol protects from apoptosis. In a female estrogen receptor knockout mouse model, glomerulosclerosis develops due to excess ovarian testosterone production. Oophorectomy preserved function and survival of podocytes. Addition of testosterone, however, resulted in podocyte apoptosis in wild-type mice that had oophorectomy. Progression in adolescents is reported, and the impact of pubertal sex hormones is a prime topic for future research.

In young adult patients with CAKUT, a GFR of less than 40 mL/minute/1.73 m^2 and proteinuria greater than 100 mg/mmol are poor prognostic indicators (**Figure 5-1**).[33] Overall rate of decline in GFR is approximately -2.4 mL/minute/year. Interestingly, in this cohort the renal outcome was similar in groups with primary renal dysplasia to those with associated abnormal bladder function. Attention to urologic management of bladder dysfunction with the goal of protecting renal function is nevertheless prudent.

FIGURE 5–1
Renal Outcome in Young Adults Stratified by Initial Degree of Proteinuria[33]

Renal outcome stratified for proteinuria (mg/mmol) at start. 10-99 vs 100-199 mg/mmol: p=0.009; 100-199 vs >200 mg/mmol: p=0.002.

Source: Neild GH, Thomson G, Nitsch D, et al. Renal outcome in adults with renal insufficiency and irregular asymmetric kidneys. BMC Nephrol. 2004;5:12.



5.3.2 Trajectory to renal replacement

CAKUT is a leading cause of CKD in children[45,62-65] and responsible for 2.2% of the cases of ESRD in adults. This rate remained relatively unchanged during the period from 1990 to 2009.[66-69] Data from European registries suggest CAKUT leads to ESRD more often in adult than in pediatric age groups, with the median age of onset of 31 years, as compared with 61 years for the non-CAKUT population, with earlier onset in male patients.[67] An underlying diagnosis of renal dysplasia also appears to be associated with earlier development of ESRD.[67]

The appearance of proteinuria and progressive renal failure indicates glomerular capillary hypertension (glomerular hyperfiltration) and progressive focal and segmental glomerulosclerosis.[70] Recent data from a national registry study of 3,198 adolescents with an underlying diagnosis of CAKUT *but with normal blood pressure and preserved renal function* reported a significantly increased risk for ESRD over a 30-year period (HR for ESRD of 4.19 (95% CI: 3.52–4.99).[71]

This highlights the importance of long-term follow-up for patients in adolescence and beyond, even with normal renal function. All patients should be managed in line with national and international guidance (https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf).[18]

The median age for reaching ESRD in patients with CAKUT is 31 years;[67] therefore, most of these patients will qualify for transplantation after age 18. One implication is that they will have different access to donor kidneys within the organ-sharing networks than those who qualify as children.

5.3.3 Pre-emptive renal transplant

Renal transplants improve quality of life and likely longevity when compared to dialysis and, where possible, pre-emptive transplant is the treatment of choice.[72] Pre-emptive transplant via living donors expands the organ pool and lowers the healthcare costs associated with dialysis. Comorbidities associated with ESRD and dialysis are avoided with pre-emptive transplantation. There are advantages in terms of patient survival, graft survival, and delayed onset of graft function and acute rejection. Socio-economic disparities in terms of access to pre-emptive transplantation and compliance with post-transplant care may bias outcomes.

Timing of pre-emptive transplant is not based upon a specific eGFR, but should be aimed toward avoiding initiation of dialysis by several months.[72] Factors beyond eGFR include biochemical findings, such as electrolytes and albuminuria-creatinine ratio, as well as overall clinical status.

Renal replacement by transplantation is discussed in detail in Section 5.4.

5.4 Relationship Between Renal Failure and Lower Urinary Tract Function

The past two sections have described means to accurately assess, preserve, and prolong renal function. It is well accepted that outlet obstruction, poor bladder compliance in neurogenic bladder, or unhealthy voiding dynamics can damage the kidneys and risk progression to CKD and ESRD.

Unfavourable interplay between the renal status and bladder function can lead to reciprocal exacerbation. The primary examples are impact of polyuria on bladder function and aggravation of existing metabolic acidosis, especially in continent urinary reservoirs created from bowel segments.

5.4.1 Polyuria

Particularly in congenital obstructive uropathy, such as PUVs, congenital and acquired tubular damage results in a urinary concentration defect.[73] Polyuria is present to varying degrees. It is not commonly physically symptomatic in terms of volume loss, but the situation may become more concerning during intercurrent illnesses with poor oral tolerance and secondary gastrointestinal losses. Polydipsia may accompany free water loss but supplemental fluids, along with supportive care of AKI, may be required during intercurrent illnesses.[73]

Aside from the need to maintain hydration as large amounts of dilute urine are produced, the volume itself can be problematic for an already dysfunctional bladder. If the bladder has borderline capacity and compliance, the urine may quickly overwhelm the functional bladder capacity. This may result in frequent need for voiding or lead to urinary incontinence. Persistent high bladder volumes in a poorly compliant system may result in upper tract dilation if the patient cannot maintain frequent-enough emptying.[73]

Polyuria and water losses can occur by a different mechanism in those with a bowel reservoir. A concentrating defect occurs across the bowel lumen in bladder augmentation and continent reservoirs made from ileum, colon, and jejunum.[74] As concentrated urine bathes the highly permeable bowel epithelium, water moves into the reservoir lumen. This movement of water results in a relative dehydration and increased urine volume.[74]

Overnight drainage with an indwelling Foley catheter allows the bladder and the upper tracts to rest overnight, is surprisingly well tolerated, and can reduce the rate of progression of CKD.[75]

5.4.2 Metabolic acidosis

Hyperchloremic metabolic acidosis results from net absorption of acid across the bowel lumen in patients where ileum or colon has been used as all or part of a reservoir.[74,76]

The surface area and dwell time influence the capacity for exchange across the bowel lumen. The mechanism is by excretion/net loss of bicarbonate through the bowel into the lumen (with absorption of chloride) and by absorption of ammonium from the urine. Ammonium appears to be the larger component. As bicarbonate is excreted, the kidney attempts to compensate for the increased acid load and ammonium is formed in the tubules. The absorption of ammonium and chloride across the bowel epithelium results in the hyperchloremic metabolic acidosis.[74] Once this buffer system is depleted, further bony buffers will be consumed. This can have implications for bone health in children and adults.[74,77] While it is not entirely clear that this acidosis would impair linear growth in children with urinary reservoirs but without CKD, somatic growth is impaired in children with acidosis related to CKD.[78] Treatment of ongoing acid load appears prudent. For patients with a pre-existing acidosis related to CKD, the situation is magnified and will require oral bicarbonate replacement.[18,79]

Regular and complete evacuation of the urine is recommended. In the face of a clinically significant acidosis (or some other clinical symptoms), an overnight Foley may be advisable for large reservoirs, with or without CKD. Conversion to an incontinent diversion (suprapubic tube or ileal conduit) may be advisable in the most severe situations.

5.4.3 Native nephrectomy and fate of the native ureters

In contrast to patients with primary parenchymal kidney disease as the cause of ESRD, patients with LUT dysfunction may have infected kidneys, high-grade VUR, marked hydroureteronephrosis, or urinary lithiasis. Affected kidneys may need to be removed prior to transplantation to control infection in the context of immunosuppression. Pretransplant native nephrectomy is not commonly required.[80] Nephrectomy is indicated for chronic infections, stones, or refractory hypertension.[80,81] Asymptomatic poorly functioning dilated systems may remain trouble-free after transplantation.

If the native kidneys excrete a substantial volume, their daily urine production helps with overall fluid management in the setting of dialysis. If it is projected that the kidneys will ultimately need to be removed, but their contribution to fluid status helps with management of dialysis and allotted daily fluid intake, one approach is to remove the left kidney first and then perform the right nephrectomy simultaneously with transplantation.[80,81]

Furthermore, consideration should be given to utility of preserving the native lower ureter if nephrectomy is required. Extensive distal dissection may result in scarring around the bladder that compromises future transplantation or reconstruction. The ureter could be used for incorporation as augmentation or as a continent catheterizable channel (CCC) in select cases. In cases where the distal ureter is healthy and intact, it remains as one option for connecting the transplant ureter to the native system.[82]

5.5 Renal Transplantation in Abnormal Lower Urinary Tract

It is estimated that 15% to 25% of pediatric patients with ESRD had congenital lower urinary tract disease and dysfunction (LUTD).[83-85] The most common LUTD phenotype is associated with a low-capacity and poorly compliant bladder. If inadequately managed, this form of bladder dysfunction will lead to obstructive nephropathy with or without primary or secondary reflux.[86,87]

5.5.1 Etiology of congenital LUT dysfunction

LUTD has a variety of neurogenic and structural causes:

- Neurogenic causes: myelomeningocele, sacral agenesis, caudal regression syndrome
- Structural causes: PUVs, high-grade reflux with inefficient emptying, urogenital sinus anomalies, bladder exstrophy and cloacal exstrophy (and/or the surgery to correct them), cloacal anomalies, and prune belly syndrome

For patients who progress to ESRD due to LUTD, the bladder or urinary reservoir will need to be evaluated and optimized by a urologist prior to receipt of an allograft in order to minimize risk for graft loss.

The goals are to have:

- Unobstructed urinary drainage from the graft into a reservoir
- A compliant reservoir with adequate capacity that stores urine at a pressure low enough to prevent reflux or damage to the allograft, for a socially acceptable time (~3 hours), and without leaking[88]
- Efficient drainage either by spontaneous voiding at a low pressure, with Valsalva assist or by clean intermittent catheterization (CIC)[89,90]

Most patients with prune belly syndrome have large-capacity, compliant bladders with no outlet obstruction, which are unlikely to impair ureteral drainage. Nonrefluxing reimplantation of the graft ureter into the bladder is unlikely to result in VUR or to cause problems to the graft.[91] The main issue in these patients is to ensure proper bladder evacuation with a low postvoid residual to decrease the risk of UTI. In general, the principle with prune belly syndrome is to maintain safety but minimize intervention to the urinary tract.

Another rare complication particular to prune belly syndrome is the torsion of the graft on its vascular pedicle. It is presumed related to the laxity of the abdominal wall, allowing graft mobility and torsion. Some form of nephropexy should be considered in these patients to minimize risk of graft injury or loss.[92-94]

When the cause of ESRD is reflux nephropathy, the presence of supravesical diversion with a long-standing defunctioned bladder does not preclude transplantation.[95] These bladders may regain function with the return of urine flow after a successful transplant. Urodynamic evaluation, with or without bladder cycling, is important in preparation for transplant in these patients. An adequate cystometric capacity and maximum flow rate (Q_{max} 18–25 mL/s) is a good indicator of success.[91]

PUV patients manifest a wide clinical spectrum of bladder phenotype, and often pose a challenge in evaluation and pre- and post-transplant management. Each potential recipient needs careful evaluation of bladder function prior to transplant. Most already have had an extensive evaluation of their bladder from the neonatal period, with the aim of slowing the decline in renal function. Optimal management may include anticholinergics, α-blockers, double or triple voiding, CIC, and/or nocturnal bladder drainage.[96]

Some PUV patients demonstrate small capacity and poorly compliant bladders that may require pretransplant augmentation cystoplasty, but some demonstrate borderline storage pressures and require surveillance and tight medical management to minimize ongoing risk to the graft. Others demonstrate a pattern of inefficient bladder contractility and incomplete emptying (further aggravated by a very high urine output as a result of impaired concentrating ability). These patients need to be followed closely post-transplant to ensure complete bladder emptying to minimize risk of recurrent infection and progressive graft deterioration.

Some children with neuropathic bladders, despite comprehensive early management, still go on to develop ESRD and require a renal transplant. This group will include those managed with anticholinergics and CIC, others who have already had a bladder augmentation, and a minority who have had temporizing supravesical diversion by an ileal conduit or a colon conduit, leaving the native bladder defunctionalized.

5.5.2 Preparation of the LUT for transplantation

It is essential to have an exhaustive evaluation of the LUT before proceeding with a transplant. An abnormal bladder can receive a transplant if appropriately evaluated and prepared medically or surgically.[97] The following elements are important:

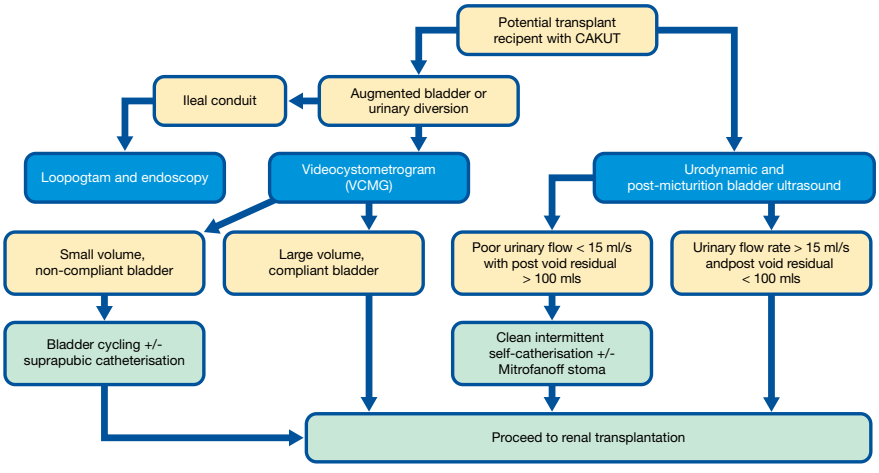
- Detailed history of LUT symptoms, including frequency-volume charts, CIC frequency, incontinence episodes, bowel and sexual history
- Occurrence of UTIs, febrile or afebrile
- Detailed surgical history
- Medications, including anticholinergics, α-blockers, botulinum toxin injections
- Presence of supravesical diversion, continent or incontinent
- Examination of the abdomen for scars and stomas and potential interference with planned surgical approach for a transplant
- Voiding cystourethrogram with urodynamic testing, or video urodynamics, to evaluate the bladder (native, augmented, or defunctioned): capacity, outlet character, presence and severity of reflux, and postvoid residual
- Upper tract imaging, most often cross-sectional imaging (CT, magnetic resonance imaging) to evaluate the native kidneys, surgical anatomy, and pelvic vasculature for surgical planning

One algorithm to help guide pretransplant assessment in patients with abnormal urinary tracts is shown in **Figure 5-2**.

FIGURE 5–2
Algorithm for Preparing the Urinary Tract to Receive Renal Transplant in Individuals With CAKUT

Figure reproduced with the permission of Dr. John Connolly.

Abbreviations: CAKUT: congenital anomalies of the kidney and urinary tract; VCMG: video cystometrogram.



5.5.3 Anatomical and physiological exclusions from renal transplant

In severe forms of caudal regression, vascular access and abnormal body configuration may preclude safe transplantation. In addition, patients with VACTERL (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities) spectrum anomalies, including cloacal malformations, mesenchymal migration anomalies, and vascular anomalies, may require substantial surgical preparation. Related medical comorbidities (eg, pulmonary compromise in PUV or congenital heart conditions) may preclude safe transplantation altogether.

5.6 Bladder Reconstruction in Renal Transplant

5.6.1 Timing of LUT reconstruction

Most authors prefer to perform bladder augmentation before any transplant to avoid the effect of immunosuppression on wound healing and to provide a safe and appropriate reservoir for the renal allograft.[98,99] In a patient who is anuric or severely oliguric, the enterocystoplasty must be irrigated daily to wash out mucus and to limit infection prior to a transplant and urine production. Furthermore, peritoneal dialysis will not be feasible after the laparotomy, and there is some risk of injury to the pedicle of the bowel segment if the renal graft is placed intraperitoneally.[100,101] If present, a Mitrofanoff channel or any other CCC is at risk for injury during preparation for graft placement. Whenever these channels are constructed, ideally they should be placed away from the anticipated placement the allograft. Often these channels were constructed years earlier before reaching ESRD and planning for transplantation. In this situation, it is advisable to have a pediatric or reconstructive urologist available to operate with the transplant team.

Bladder reconstruction can also be performed after a patient has been transplanted. It has the advantage of performing the reconstruction after restoring renal function (and hence urine production), thus avoiding the problems associated with dry cystoplasty. The pedicle to the augmentation will not be at risk. However, there will be some problems with the administration of oral immunosuppression in the first postoperative days. The transplant ureter may be at risk during augmentation or placement of a continent channel. It may not be identified due to adhesions or it may be devascularized when it is dissected free from a skin ureterostomy to be reimplanted in the bladder.[98]

Simultaneous bladder augmentation and kidney transplantation have been previously reported in a limited number of patients.[102-104] Data suggest that the potential gains of a single procedure, however, do not justify the hazards of such a lengthy complicated procedure and recovery, with fluid shifts, immunosuppression, high risk of infections, and delayed wound or anastomotic healing.

There are some situations where the difficulties encountered post-cystoplasty will be challenging for the patient but the bladder function is considered borderline. It may be possible (in some) to avoid an augmentation, and therefore a reasonable approach may be to monitor the bladder and renal function closely for hostility or deteriorating renal function following a transplant.[86,105]

Living related grafts offer the advantage of the ability to arrange LUT reconstruction at a planned time before transplantation, as in the situation of pre-emptive transplantation (see section 5.2 of this chapter). With deceased donor grafts, however, restoration of the LUT should be completed before inclusion on the waiting list.

5.6.2 Bladder augmentation

If urodynamics demonstrate the inability to achieve a bladder capacity greater than 75% of the expected with pressure below 30 cm H_2O, bladder augmentation is indicated.[106] A variety of substrates and techniques have been described to improve capacity and compliance and accept the transplant.

Enterocystoplasty, using a segment of detubularized ileum, ileocecum, sigmoid, or stomach, is the most common form of bladder augmentation. Because of extensive experience with its use and relatively acceptable side effects, detubularized ileum is the most popular. Sigmoid has the advantage of tenia coli to facilitate antireflux ureteric reimplant, but it should be used with caution in neuropathic conditions and in other types of anal sphincter dysfunction, as the patient may subsequently experience changes in bowel habits and fecal incontinence. The ileocecal segment can be used, with the detubularized cecum for augmentation, its tenia for ureteric reimplant, and the terminal ileum as a cutaneous CCC, as in some bladder exstrophy cases with a poor bladder and persistent incontinence or difficult CIC per urethra.[89,107,108] The ileocecal segment also should be used with caution in the neuropathic population due to potential for rapid transit of loose stool. Additionally, resection of the terminal ileum impacts absorption of bile salts and vitamins. Impaired absorption of the vitamin B12 intrinsic factor complex can result in a variety of complaints, including subacute combined degeneration of the cord—an irreversible neurological deficit.

Gastrocystoplasty offers several advantages over ileum, such as the absence of mucus production, decreased bacteriuria, no aggravation of acidosis in patients with CKD, and decreased absorption of chloride. However, the occurrence of hematuria-dysuria syndrome created marked discomfort in some individuals with sensate urethra and/or incontinence.[109,110] Cincinnati Children's Hospital Medical Center surgeons describe the use of stomach, particularly in cloaca, cloacal exstrophy, and anorectal malformation where small bowel cystoplasty may be contraindicated due to short gut physiology. The use of colon may be contraindicated because it may compromise fecal continence, or it may risk vascular injury to the reconstructed anorectum, which depends on descending blood supply.[80] Reports of gastrocystoplasty in renal transplant patients, however, are limited.

Ureterocystoplasty is a more physiological alternative in patients with markedly dilated ureters, although availability of a dilated orphan ureter for this option is rare. Due to jeopardized blood supply, patients with previous ureteric reimplant are not appropriate candidates for ureterocystoplasty.

Reported results regarding ureterocystoplasty have been mixed.[90] In a review study by Gonzalez and Ludwikowski on the alternatives to enterocystoplasty, they describe all conceivable variations of ureterocystoplasty, including use of the lower ureter only or the entire ureter, whether unilateral or bilateral, with gratifying results.[111] This same study included a more conservative multi-institutional viewpoint by Husmann *et al.*, who noted that ureterocystoplasty is most effective when the ureters were nonrefluxing with a diameter of >1.5 cm and the whole ureter was used. In refluxing ureters, it is effective only when the whole system (bladder + ureters) has a reasonable capacity and compliance.[112] Effectively, beyond reconfiguring the system, nothing is gained urodynamically in the refluxing system. None of these studies included transplanted patients.

Nahas and associates reported good results in 21 augmentation cystoplasties performed in preparation for transplant.[89] This study included 14 enterocystoplasties and 7 ureterocystoplasties, of which 2 failed and required correction with ileum.

Other procedures reported to augment the bladder include detrusorotomy/detrusorectomy, covered detrusorectomy, or seromuscular colocystoplasty lined with urothelium. These less traditional procedures, however, cannot be relied on to correct the bladder capacity and compliance in preparation for transplant.[89,107,108]

5.6.3 Permanent incontinent diversions

With the development of innovative LUT reconstructive techniques, the need for long-term diversion is limited. It is reserved for those with the most complex anatomy, with or without short gut, including severe cases of caudal regression or cloacal exstrophy, and for patients who cannot perform CIC per urethra or per catheterizable channel.[113] Incontinent ileal and sigmoid conduits have been used extensively. When treating young patients with congenital anomalies, conduits would be used less commonly, although these diversions are still widely applied in uro-oncology and certainly have a place for some congenital patients.

5.7 Continence and Other Facets of Bladder Management

Maximum benefit from renal transplant is not achieved if the patient is troubled with unresolved urinary incontinence.[91, 114] This is mainly seen in bladder and cloacal exstrophy patients and in some neuropathic bladders with very low outlet resistance. Continence can be achieved through bladder neck reconstruction, bladder neck closure, placement of a sling, or implantation of an artificial sphincter. There are, however, limited reports on the use of artificial sphincters with transplants due to concerns about infection.[115,116] Diversion by conduit prior to a transplant remains an option for cases not suitable for outlet reconstruction, if a major reconstruction is not embraced by the patient, or if reconstruction is not medically prudent.

5.7.1 Clean intermittent catheterization

In patients who are unable to void or who cannot void safely or efficiently, catheterization must be introduced prior to a transplant. It is essential to ensure that the patient (and care network) is fully aware of the importance of CIC to empty the bladder or reservoir in order to: reduce infections, attain safe storage pressures, and achieve continence. The transition period between augmentation and transplant can be used to adjust to CIC. Sensate boys may be resistant to urethral catheterization and may be better served by a CCC. The same applies to girls who use a wheelchair or whose body habitus makes hygiene and self-catheterization challenging.

5.7.2 Bladder cycling

Bladder cycling is mainly used in defunctioned bladders to assess (and improve) capacity, compliance, and voiding properties. It is accomplished through instillation of increasing volumes of saline into the bladder through a small percutaneously placed suprapubic tube or through catheterization. Volume increments and time kept are usually determined empirically, depending on the patient feeling the need to void or until leakage occurs. Antimuscarinic agents can be added to expand volume and compliance. This may be a good time to introduce the patient to CIC.

5.8 Graft Survival in the Setting of Congenital Urogenital Anomalies and Reconstructed Urinary Tract

The first renal transplant into an ileal conduit was performed in 1966,[117] just 12 years after the first successful isograft between identical twins was performed in Boston in 1954. In 1971, successful renal transplantation in children with rehabilitated LUT abnormalities was reported.[118] In 1982, Marshall *et al.* performed pyelo-ileocecocystoplasty for the first time in a patient after renal transplant.[95] This was followed by the first pediatric renal transplant into an augmented bladder in 1984.[119]

Early publications showed a statistically significant difference in graft survival between those with congenital uropathy, particularly PUVs, and those with a normal LUT. In more recent series, with rehabilitation and/or reconstruction of the LUT, namely by bladder augmentation, comparable graft survival was achieved between those with LUT dysfunction and those without (**Table 5-4**). However, patients with LUT dysfunction have a higher incidence of UTIs, VUR into the allograft ureter, and graft dysfunction at 5 years or more post-transplant, as measured by higher serum creatinine or diminished GFR (**Figure 5-3**).[120] In a large experience from the Institute of Urology and Nephrology of University College London, in London, United Kingdom, evaluating transplants in adults with abnormal bladders, there was no difference in 10-year graft survival between patients with renal dysplasia and normal bladders (61%) compared to those with augmented bladders or urinary diversions (66%). However, longer-term follow-up did show an advantage in graft survival for patients with normal bladders.[121]

Interpretation of the studies is difficult since they are all retrospective, some of them lack a control arm, and the majority have a relatively small number of heterogeneous cases (**Table 5-4**).

TABLE 5–4 Graft Survival in the Setting of Congenital Uropathy and Reconstructed Urinary Tract

Author	No./Patients	Graft Survival, % at (n) Years	Controls	Graft Survival, % at (n) Years	Significance
Churchill *et al.* 1988[122]	13/PUVs No Augment	35 (5)	Reflux N.U.	70 (5) 75 (5)	s s
Reinberg *et al.* 1988[123]	18/PUVs No Augment	50 (5)	Reflux (18) N.U. (36)	73 (5) 75 (5)	ns
Indudhara *et al.* 1998[124]	18/PUVs No Augment	54 (10)	N.U. (18)	41 (10)	ns
Salomon *et al.* 1997[120]	66/PUVs	69 (5) 54 (10)	GU anomalies* No LUTD (116)	72 (5) 50 (10)	ns
Fontaine *et al.* 1998[125]	14/10 PUVs 14/Augmented	84 (5) 73 (10)	N/A	-	N/A
Hatch *et al.* 2001[126]	20 LUTD 10 No LUTD	78 (5) 60 (10)	N/A	-	N/A
Adams *et al.* 2004[32]	27/PUVs 7/Prune belly 4/Neurogenic 28/Reflux	62.9 (5) 71.4 (5) 50 (5) 78.5 (5)	N/A	-	ns
Taghizadeh *et al.* 2007[98]	16	88.9 (5) 66.7 (10)	N/A	-	N/A
Nahas *et al.* 2008[127]	19	84 (5)	N.U. (136) No LUTD (56)	75 (5) 74 (5)	ns
Saad *et al.* 2016[105]	29 LUTD (12 PUVs)	96 (3)	74 No LUTD	97 (3)	ns (p=1.00)

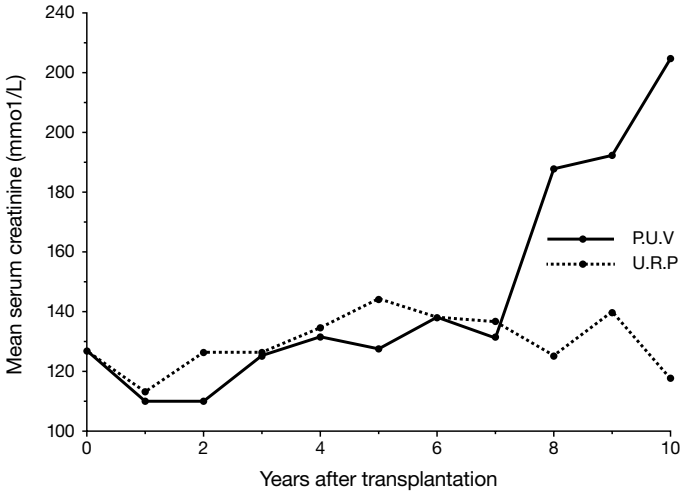
Abbreviations: GU: genitourinary; LUTD: lower urinary tract disease and dysfunction; N/A: not applicable; ns: nonsignificant; NU: not urologic; PUV: posterior urethral valve; s: significant.

*Vesicoureteral reflux, megaureter, ureteropelvic junction obstruction.

FIGURE 5–3
Mean Serum Creatinine in PUV and Non-LUTD Genitourinary Anomalies[120]

Abbreviations: LUTD: lower urinary tract disease; PUV: posterior urethral valve; URP: malformation uropathy = vesicoureteral reflux, megaureter, ureteropelvic junction obstruction.

Source: Salomon L, Fontaine E, Gagnadoux MF, et al. Posterior urethral valves: Long-term renal function consequences after transplantation. J Urol. 1997;157(3):992–995.



5.9 Effect of Immunosuppression on UTI Risk

UTI is a common complication following renal transplant, with an overall incidence of 0.45/1,000 transplant days. The flora observed in urine cultures of transplant patients is varied. The prevalence of multidrug-resistant organisms is increasing. The distinction between asymptomatic bacteriuria and symptomatic infection or recurrent infections is important, as asymptomatic bacteriuria may not need treatment, even in the setting of immunosuppression.[128]

Most UTIs occur within the first 6 months following transplant. In a large, multicentre study in Spain, 37% occurred in the first month, 47% between 2 and 6 months, and 16% more than 6 months after transplant.[129] Most triple therapy immunosuppressive protocols have not been associated with an increased incidence of UTIs. However, more bacterial infections were found in patients who received antithymocyte globulin versus those who received basiliximab, and in patients who received sirolimus versus those who received tacrolimus.[130]

In another study, acute pyelonephritis was most strongly correlated with prior therapy for acute rejection.[131] Patients with a serum creatinine level of more than 2 mg/dL, daily prednisone of more than 20 mg, and multiple rejection therapies are also more prone to having infections, even after the first 6 months post-transplant.[132]

Most recent studies demonstrate similar patient and graft survival rates in patients with and without post-transplant UTIs. It seems that serum creatinine or GFR may be a more sensitive and fair indicator of the impact of UTIs on graft function now that overall graft survival is higher on modern medical regimens. Furthermore, if only episodes of pyelonephritis are considered, the difference in impact on the graft would be even more pronounced.[133]

Among patients with LUT dysfunction, PUV patients are the most vulnerable. Post-transplant UTIs occur with a considerably greater frequency in valve bladder recipients (**Figures 5-4 and 5-5**).[134] This may be related to incomplete emptying and/or borderline intravesical pressure, although others have not seen association with bladder dysfunction.[133] Nevertheless, valve bladder patients require close follow-up to detect any upper tract changes. They nee/td frequent bladder emptying; some of them may require CIC and/or nocturnal catheterization to protect the graft from high bladder pressure, to decrease urine dwell time, and to reduce risk of febrile UTIs.

Antimicrobial prophylaxis is now standard practice in most transplant centres. Trimethoprim-sulfamethoxazole (TMP-SMZ) is the most commonly used due to its activity against *Pneumocystis carinii*. TMP-SMZ was found to significantly reduce post-transplant UTI by 50% in prospective randomized trials.[135]

FIGURE 5–4
Percentage of Children With UTI After Transplantation PUV Versus Controls ($p<0.05$).[134]

Abbreviations: PUV: posterior urethral valve; UTI: urinary tract infection.

Source: Mochon M, Kaiser BA, Dunn S, et al. Urinary tract infections in children with posterior urethral valves after kidney transplantation. J Urol. 1992;148(6):1874–1876.

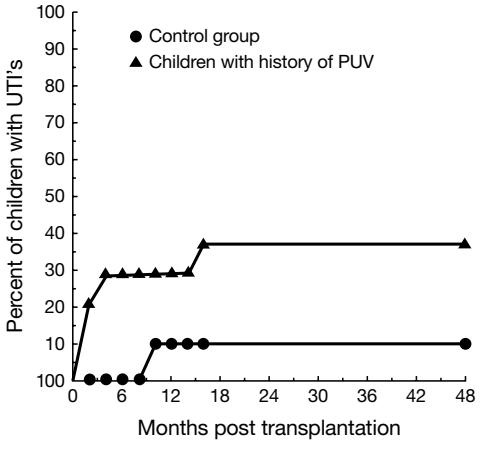
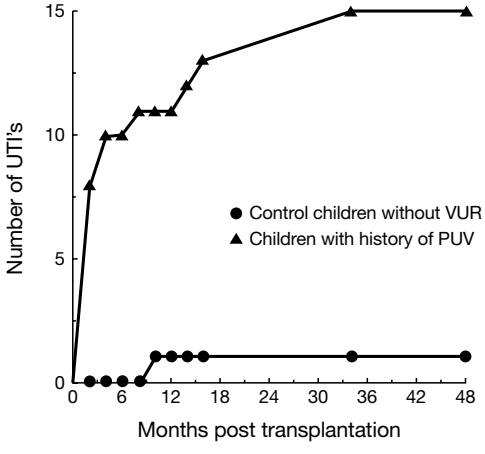


FIGURE 5–5
Number of UTI Episodes After Transplantation PUV Versus Control ($p<0.01$).[134]

Abbreviations: PUV: posterior urethral valve; UTI: urinary tract infection VUR: vesicoureteral reflux.

Source: Mochon M, Kaiser BA, Dunn S, et al. Urinary tract infections in children with posterior urethral valves after kidney transplantation. J Urol. 1992;148(6):1874–1876.



5.10 Management of Upper Tract Urolithiasis in the Congenital Genitourinary Diseases

When congenitally anomalous kidneys form stones, the management can prove challenging. Specific upper tract anomalies that present the greatest difficulties are the anomalies of renal ascent, including simple renal ectopia, and the anomalies of form and fusion, such as horseshoe kidneys and crossed renal ectopia with or without fusion. Although it is not strictly a congenital genitourinary anomaly, stones in autosomal dominant polycystic kidney disease (ADPKD) can present similar complexities and challenges in stone management.

Despite aberrant anatomy, treatment of stones should follow the same guidelines and principles as for normal kidneys, with slight but necessary modifications. Treatment of individual patients differs depending upon the size and location of the stone, as well as function, location, and anatomy of the kidney and LUT.

5.10.1 Etiology and pathogenesis of stone formation in anomalous kidneys

Ectopic kidneys occur slightly more commonly on the left than the right. The location of an ectopic kidney can be pelvic, iliac, abdominal, or thoracic, and may be crossed/crossed-fused. Most ectopic kidneys also display an element of malrotation, usually resulting in a relatively anterior position of the renal pelvis.[136] This predisposes the patient to stone formation due to the alteration in spatial orientation of the pelvis with respect to the calyces. Depending upon the specific anomaly, the ureters often are tortuous, which can further impair urine drainage. Additionally, ectopic kidneys are characteristically associated with aberrant vessels; these may be single or multiple and are commonly derived from the distal aorta/aortic bifurcation or the iliac vessels. Aberrant vasculature may provide additional challenges—predisposing to stone formation by impairing pelvic drainage (as with crossing vessels) or limiting percutaneous access—especially for lower pole stones.[136,137]

Horseshoe kidney is the most common congenital anomaly of the urinary tract (1:400 births) and is more common in males (2:1). In 95% of cases, fusion is at the lower poles.[138] They are in a lower than normal position and incompletely rotated. The calyces are normal in number but have atypical orientation. Most of the calyces point posteriorly, and the lower pole calyces point caudally and medially.[139] The malrotation of the fused kidney causes the insertion of the ureters to be superior and lateral ("high insertion"). As a final point, because the ureters have to transverse over the renal isthmus, their course is deviated anteriorly several centimetres below the actual UPJ, which can result in stasis. Suboptimal drainage occurs in up to 35% and recurrent UTI in up to 41% of horseshoe kidney patients. The mean reported incidence of stone formation in horseshoe kidneys is 20% to 40% (range 1%–67%).[138,140]

Besides these anatomical abnormalities, metabolic abnormalities are reported in 16% to 100% of anomalous kidneys. Raj *et al.* reviewed 11 patients with horseshoe kidneys and identified metabolic abnormalities in all.[141] Compared with a group of stone-formers with normal renal anatomy, those patients with horseshoe kidneys exhibited a similar distribution of metabolic derangements, the most common being low urine volume, hypercalciuria, and hypocitraturia. Hypocitraturia was markedly overrepresented (55% in the patients with horseshoe kidneys vs 31% in controls). It seems clear that although urinary stasis likely contributes to a propensity toward stone formation in patients with anomalous kidneys, an underlying metabolic abnormality is required for stone formation to occur.[141]

5.10.2 Evaluation and management of stone disease

The key imaging modalities to be employed include ultrasound of the abdomen and computed tomography (CT). On-table ultrasound by the surgeon may facilitate surgical decision-making. For instance, if a good acoustic window is seen while scanning an ectopic pelvic kidney, it suggests that an ultrasound-guided puncture is possible.[142] A CT characterizes the stone: size, location within the renal pelvis or calyces, and density by Hounsfield units. This information can dictate the treatment modality to be used,[143] reveal the number of stones (may be difficult with an ultrasound), and assess the skin-to-stone distance that is important, especially in obese patients.

It is important to understand the relationship of anomalous and ectopic kidneys with the surrounding structures and organs. Ectopic kidneys might be located within the pelvic brim, and small bowel loops might obscure safe percutaneous access. Horseshoe kidneys also have a higher incidence of retrorenal colon, due to a defect in the development of lateral fascia with resultant deficiency of mechanical support to the colon.[144] Maheshwari *et al.* have shown that contrast-enhanced CT can identify major vessels entering the kidney along the posterior surface.[145] In this situation, the findings of a contrast CT scan forced surgeons to alter the final treatment modality for stone clearance. It is clear that CT can help in planning punctures in anomalous kidneys. Additionally, a preoperative CT has the advantage of predicting the outcome of extracorporeal shock wave lithotripsy (ESWL) treatment with or without multiple or auxiliary procedures, or effectiveness quotient, by consideration of stone density, stone volume, and skin-to-stone distance (Triple D score).[143,146,147] Ectopic kidneys pose a problem for any planned intervention due to their anomalous blood supply, as discussed in the preceding sections. These kidneys are prone to iatrogenic injuries because of their varied vasculature and anatomical relationships. These complications can be avoided or reduced by preoperative CT planning with angiography.[148,149] A preoperative CT is strongly recommended in ectopic kidneys, and surgical management may be best in the hands of expert endo-urologists.

5.10.3 Treatment considerations in ectopic kidneys

5.10.3.1 Percutaneous nephrolithotomy

Percutaneous nephrolithotomy (PCNL) is a well-established technique for the treatment of urolithiasis in normal kidneys and is often used as first-line treatment in horseshoe kidneys, especially when calculi are larger than 2 cm or after failed ESWL.

Access to the pelvicalyceal system can be gained with ultrasound,[142] fluoroscopic-assisted, laparoscopic-assisted,[150-152] or any combination of these methods. In the experience at Muljibhai Patel Urological Hospital (MPUH) in Gujarat, India, the routine practice has been to use either just ultrasound alone or in combination with fluoroscopy. Pressure with the ultrasound probe helps in displacing the bowel and thus avoids bowel injuries, which can be a major concern in ectopically placed kidneys.

Having gained access, further expertise is needed to ensure safe dilatation: the patient is more commonly supine (as opposed to prone) and the direction of the tract may vary, necessitating greater care than in a prone procedure with a normal kidney. The location of the kidney decides the length of the tract. Pelvic kidneys are often deeper than orthotopic kidneys and may necessitate longer Amplatz sheaths, instruments, and nephroscopes. Associated vascular anomalies and malrotation can lead to a substantial bleeding risk if not identified preoperatively, as access to these kidneys is typically ventral. A colour Doppler done alongside the ultrasound access can circumvent this issue in routine clinical practice (**Figures 5-6 and 5-7**). Various series have reported a high success rate of 77% to 86%, with very minimal need for additional procedures after stone clearance.[142,153,154]

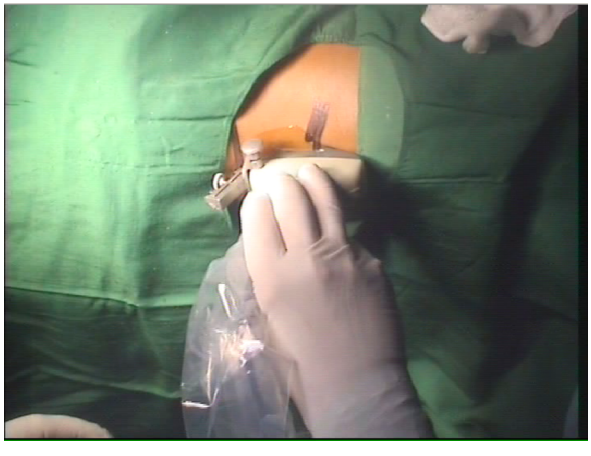


FIGURE 5–6
The landmarks to access the ectopic kidney have been established. Doppler ultrasound guidance during access minimizes vascular and bowel injury. Image was reproduced with the permission of Dr. Arvind Ganpule and Dr. Mahesh Desai.

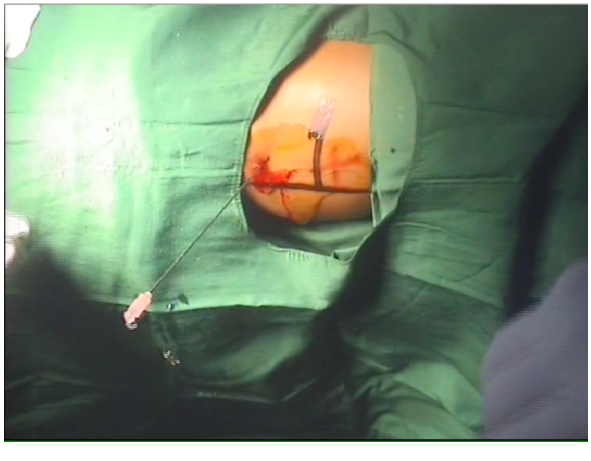


FIGURE 5–7
Percutaneous access to the ectopic kidney is complete and tract dilation will begin.

Image was reproduced with the permission of Dr. Arvind Ganpule and Dr. Mahesh Desai.

5.10.3.2 Laparoscopic-assisted PCNL

Laparoscopic-guided treatment of stones in pelvic kidneys permits visual exposure of the kidney, enhancing safe puncture and correct tract placement that is integral to PCNL.[155] Laparoscopic-assisted PCNL for the treatment of stones in a pelvic kidney was first described by Eshghi *et al.*[150] Additionally, laparoscopic/robotic nephrolithotomy is possible, both by transperitoneal and retroperitoneal approach, which can clear complete staghorn stones, as well. Laparoscopic pyelolithotomy is also possible for large burden renal pelvis stones.[156-158]

5.10.3.3 Flexible ureteroscopy

Varied ureteric insertion and ureteric tortuosity and angulation are potential obstacles to flexible ureteroscopy (FURS). Placement of a ureteral access sheath is invaluable, as it straightens the ureter and allows easy passage of the ureteroscope and egress of the fluid and fragments with faster clearance. Miniaturization of scopes, availability of slender and powerful lasers, and development of smaller accessories like nitinol baskets have improved stone clearance rates.[162] Although success rates are in the range of 65% to 80%, more staged procedures may be required than in orthotopic kidneys, and proper case selection is the key for maximal stone clearance.[154,160-162]

5.10.3.4 Extracorporeal shock wave lithotripsy (ESWL)

Anatomical relationships to the ectopic kidney can be responsible for limitations in successfully treating stones with ESWL. Spine and pelvic bones obscure the location of stones in medial calyces. The associated malrotation makes it more difficult to precisely localize the stone and accurately focus shock waves. The resultant scatter of energy may lead to inadequate fragmentation. Patient position can influence stone localization (more than in other scenarios) and if the prone position is not possible, then the patient can be placed in a supine position.

Upper urinary tract anomalies, such as incomplete rotation, high insertion of the ureter, tortuosity of the ureter, and variation in vascular anatomy, hinder drainage and promote stasis; hence, the likelihood of success is decreased with ESWL. Measures that may overcome these difficulties are routine placement of stent, delivery of shocks at high power, and identification of the ideal positioning for each patient based upon the stone location and ultrasound findings. Although they may help, these measures increase the success rates only marginally, and overall success rates of ESWL for ectopic kidneys remain low (55%–67%) in various series.[163,164]

5.10.4 Treatment consideration in horseshoe kidneys

Endourological management of calculi in horseshoe kidneys is the accepted gold standard, but the specific endo-urologic approach requires careful evaluation and judicious planning.

5.10.4.1 Percutaneous nephrolithotomy

Percutaneous access is generally easier in horseshoe kidneys than in orthotopic kidneys, as the superior calyces are lower and can be punctured by subcostal approach. Anatomically, the pelvis is ventral and the calyces are dorsomedial, which mandates the entry site to be more medial than usual for direct entry into the posterior calyx. Although the vascular anatomy is variable with many aberrant vessels to the isthmus region, most of these are anterior and usually there is no abnormal vascular structure posterior to the superior calyx.[140,165]

Access can be gained by using ultrasound and/or fluoroscopy, and the direction and techniques are no different from an orthotopic kidney. The tract may be longer and mandate longer instruments.[138] Use of a flexible nephroscope may avoid unnecessary lower calyx punctures and their antecedent complications.[166] High clearance rates (88% in MPUH experience) and lower retreatment rates, despite larger stone burden and multiplicity, can be achieved. PCNL is the established gold standard for larger stone burden (>2 cm), with many series showing success rates of >80%.[141,166,167] Miniaturized percutaneous stone techniques such as Miniperc and Microperc may be attractive options for smaller stones, instead of FURS. The complication rates reported are also comparable with PCNL in normal kidneys; minor complications, such as hematuria and infection, occur in 15%, and major complications, such as hydropneumothorax requiring insertion of a chest drain, occur in 2%.[168]

5.10.4.2 Flexible ureteroscopy

FURS is an attractive option for smaller stone burden, albeit at slightly lower success rates (75%–80%).[159] Retrograde FURS is used more frequently, especially for stones less than 15 mm in diameter, using the holmium laser for stone disintegration. The proposed reasons for lower success rates are:

- Difficulty with ureteric access
- Decreased scope manoeuvrability due to bending at the anteriorly displaced UPJ
- Improper case selection with larger stone burden
- Impaired drainage due to anatomical factors

The MPUH series (contributing authors Dr. Mahesh Desai and Dr. Arvind Ganpule) showed a lesser clearance rate (80% vs 88% with PCNL) with similar retreatment rates.[167]

FURS had a distinct advantage, however, in obese patients, in patients with bleeding diathesis, and in those with poor cardiopulmonary status who could not tolerate a prone position or laparoscopic procedure.

5.10.4.3 Extracorporeal shock wave lithotripsy

As described for ectopic kidneys, horseshoe kidneys may not be ideal for treatment with ESWL. The skin-to-stone distance is often increased, resulting in difficulty accurately focusing on the stone. The anterior position of the pelvis in horseshoe kidneys precludes the precise localization of the stone, leading to inadequate fragmentation. Stones in medial calyces may be obscured by the spine. Intrinsic anomalies such as incomplete rotation, posterior location of the pelvis, fused lower poles, high insertion of the ureter, and variation in vascular anatomy hinder drainage and ultimately the success rates. The overall success rates are in the range of 66% to 76%, at best.

Anomalies of ascent, form, and fusion can present challenges in stone management. A good understanding of the unique anatomy and the stone characteristics will help guide the selection of treatment modality while achieving appropriate stone clearance rates and minimizing complications. The most complex cases may be referred to more experienced endo-urologists for specialized care.

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C6

Age-Related Urologic Problems in the Complex Urologic Patient

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Committee 6

CONTENTS

Age-Related Urologic Problems in the Complex Urologic Patient

6.1 Introduction

Patients with congenital abnormalities, or complex urologic conditions, now live longer than ever before, and have healthier lives as a result of advances in medical care throughout childhood and adolescence. As a consequence, these patients are more likely to develop common, age-related urologic conditions that affect the general population. However, medical guidelines and most publications do not consider that investigation and treatment of these conditions should be adapted for patients with complex needs. Furthermore, these patients will seek to start families and may need assistance with fertility, and subsequent pregnancy, from healthcare professionals with the appropriate expertise. This chapter will consider some common, age-related conditions and available evidence, and, where lacking expert opinion, make recommendations to guide future care for these patients.

6.2 Benign Prostatic Hyperplasia and the Neurogenic Bladder

6.2.1 Overview of existing literature and how patients with neurogenic bladder may differ

The literature is sparse regarding the prevalence and management of benign prostatic hyperplasia (BPH) in men with neurogenic bladder (NGB). This overview provides a brief review of the existing literature on this topic, much of which is expert opinion due to a lack of scientific data, then subsequent sections will provide more detailed insights.

A 2001 study by Knutson *et al.* examined the coexistence of BPH with overactive bladder (OAB) and briefly mentioned how these issues may present in patients with neurologic conditions.[1] Patients with neurologic conditions were excluded from the final analysis; roughly 55% of men in the study had isolated obstruction from BPH, whereas 45% had both obstruction and concomitant OAB. This latter group offers a theoretical view of what may be seen in patients with neurogenic overactivity and BPH—that is, a greater risk of urge urinary incontinence following outlet procedures. BPH may induce OAB, which may become increasingly prevalent in aging patients with congenital urologic issues.

In *Textbook of the Neurogenic Bladder,* Blavias and Sidhu specifically addressed this topic and noted that such typical urologic conditions may be as likely in neurogenic patients as in the non-neurogenic population[2]; however, conclusive data is lacking.[3]

Hartman and Firoozi addressed prolapse and BPH in patients with NGB.[4] They presented a number of scenarios to illustrate the possible presentations of BPH: difficulty catheterizing or pain in men dependent upon clean intermittent catheterization (CIC); Valsalva or Credé voiding with increasing and symptomatic post-void residual bladder volumes; more frequent urinary tract infections (UTIs); hematuria; and onset of lower urinary tract symptoms (LUTS) that would otherwise be expected in men of similar age. The authors noted that prudent diagnostic considerations should include changes related to anatomy (such as weight gain) or the effect of prior treatment, including augmentation cystoplasty, and a predisposition to stone formation. One long-term study by Husmann of 75 male and female patients with spina bifida (SB) who had augmentation cystoplasty over a 25-year period showed bladder stone formation in 50% and renal deterioration in 38%, with poorer outcomes related to poor compliance with intermittent catheterization irrespective of the study population.[5] Hartman and Firoozi also discussed management options, which are included in the management section (**Section 6.2.4**).

Palleschi and Al Salhi, in *Bladder Outlet Obstruction in Neurogenic Patients,* focused upon surgical treatment of BPH in this patient population.[6] They briefly discussed spinal cord injury (SCI), but otherwise focused upon neurodegenerative disorders. There was an emphasis on the potential for developing postoperative complications, including incontinence, which may leave a patient in worse condition than before surgery. Overall, a focus on preserving quality of life (QoL) and diagnostic

testing to minimize procedural risk were emphasized in this text; however, they presented no data to support this. A study looking at how bladder-emptying methods impact the QoL in a neurogenic population showed that higher age and a dependence on indwelling catheters (urethral greater than suprapubic) were associated with the greatest impact on QoL.[7]

Corcos and Przydacz focused specifically upon BPH in NGB, and provided estimates of BPH prevalence in the general population, alongside acquired and congenital etiologies of NGB.[8] They provided recommendations for careful diagnostic testing, emphasizing the need for urodynamics—at times with fluoroscopy—to delineate whether a man's symptoms are neurogenic or anatomic in nature.

Noordhoff *et al.* provided a systematic review of bladder outlet obstruction surgery in NGB.[9] The review screened a large number of studies and ultimately narrowed the review to eight publications, which included investigations in bladder neck contracture; BPH; and urethral stricture in patients with NGB secondary to neurodegenerative disease, stroke, SCI, and a few cases of congenital conditions. No clear conclusions were possible secondary to the heterogeneous nature of the studies. However, some helpful general observations were made, especially regarding trans-urethral resection of the prostate, as detailed in subsequent sections (**Section 6.2.4.2**).

6.2.2 Upper tract deterioration

A key objective when managing adolescents and adults with congenital urological conditions is to preserve and maintain renal function. A clear understanding of the underlying diagnosis and previous medical and surgical history is essential. Often, detailed medical information can be difficult to obtain as patients have moved across services; however, once collated, this information should be shared with all of the patients' healthcare teams.

6.2.2.1 Measurement of renal function

Renal function should be tracked across the patient's lifespan and, especially closely, around the time of transition to adult care. Baseline renal function assessment should include blood measurement of serum creatinine and the calculation of an estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) formula.[10]

$$GFR\ (mL/min/1.73\ m^2) = 175 \times (S_{cr})^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

The accuracy of MDRD in non-weightbearing patients has not been demonstrated.

In children, including teenagers, the Bedside Schwartz equation can be used.[11]

$$GFR\ (mL/min/1.73\ m^2) = (0.41 \times \text{height in cm}) / \text{creatinine in mg/dL}$$

Significant growth during young adult life, especially with an increase in muscle bulk, can affect the interpretation of trends in serum creatinine and eGFR results. Where such difficulty in measurement of weight exists due to mobility issues or patients with neurological conditions affecting muscle mass, a more direct and accurate measurement of GFR is appropriate. Creatinine-based estimates of GFR

have not been shown to be accurate in non-weightbearing individuals. Gold standard iohexol clearance is rarely used in clinical practice; instead nuclear medicine GFR measurement with chromium-labelled ethylenediaminetetraacetic acid (EDTA) provides excellent results.[12]

The rate of change and/or decline in renal function is as important as the actual measured GFR. This is best assessed over a period of months with serial assessments of eGFR.[13] eGFR provides a better assessment of the rate of change than measuring serum creatinine, particularly in patients with significantly reduced renal function, as changes in eGFR tend to be linear, whereas changes in creatinine become exponential.[14]

6.2.2.2 Markers of renal disease

Additional markers of renal deterioration include hypertension and proteinuria. Blood pressure should be measured routinely with an appropriately sized sphygmomanometer, and urine should be tested for the presence of protein.[15,16] If proteinuria is detected by dipstick test, it should be quantified by urine protein:creatinine ratio measurement. In the absence of urine infection and/or an augmented bladder with a bowel segment, proteinuria is a significant marker of renal disease.[17] It is also modifiable and a reduction in proteinuria can be associated with the stabilization of a decline in renal function. There is an important role for angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARB) in treating proteinuria and hypertension. Both drugs act via the renin-angiotensin pathway on postglomerular (efferent) arterioles, decreasing postglomerular vascular resistance and decreasing intraglomerular hypertension. This, in turn, leads to a decrease in intraglomerular filtration pressure and, therefore, decreases proteinuria. These agents may also lead to glomerular remodelling, stabilizing renal glomerular filter damage. Reducing proteinuria itself may reduce a negative inflammatory effect on the nephron.[18] Hypertension should be preemptively and appropriately treated to prevent end-organ damage.[19]

With a decrease in renal function, acid-base imbalance can occur. This can be compounded in patients with bowel segments incorporated into the urinary tract, particularly in continent urinary reservoirs, where the urine dwell time permits absorption of H^+ across the epithelium. Hyperchloremic metabolic acidosis is most often seen in this scenario.[20] Serum bicarbonate and chloride levels should be regularly measured in these patients and corrected to normal levels with appropriate oral sodium bicarbonate supplements.

6.2.2.3 Monitoring of upper tracts for post-renal causes of renal disease

It is vital to regularly assess upper tracts,[13] and to appreciate the interaction between lower and upper urinary tracts in patients with congenital NGB. Subsequent serial monitoring for post-renal causes of renal disease can provide an early warning sign of an impending decrease in renal function. Ultrasound is used in first-line assessment as it is noninvasive and provides a wealth of information in assessing the entire urinary tract, especially when performed prior to and after bladder emptying. Worsening hydronephrosis, particularly if persisting after the patient has voided, and increasing post-void residuals are key findings.

Other imaging modalities used in monitoring changes in the upper urinary tract include nuclear medicine scans: dimercaptosuccinic acid (DMSA) provides accurate information relating to dividing (split) renal function and also the presence, position, and extent of renal scarring. Nuclear medicine

renography with technetium-labelled mercaptoacetyltriglycine-3 (MAG-3) or diethylenetriamine pentaacetic acid (DTPA) provides dynamic information relating to upper tract drainage, especially when integrated with a diuretic challenge, such as a furosemide challenge of 15 minutes (f-15) prior to MAG-3 injection.

The interaction of lower and upper urinary tracts in the case of vesicoureteral reflux (VUR) is best investigated radiologically with voiding cystogram, either as a stand-alone micturating cystourethrogram (MCUG) or in combination with a cystometrogram, which is part of video urodynamics. VUR can also be assessed more indirectly with nuclear medicine MAG-3, indirect MCUG, and microbubble ultrasound scans.

Video urodynamics are the cornerstone of lower urinary tract assessment, measuring bladder filling pressures, bladder compliance, bladder capacity, voiding pressures, and bladder emptying. However, without concurrent radiologic visualization of the upper tracts, high pressure being transmitted to the upper tracts via reflux cannot be ruled out. This complex scenario can be better investigated when urodynamics is performed with and without ureteric balloon occlusion catheters.[13,21,22]

Cross-sectional imaging of the upper and lower urinary tracts may be necessary in certain scenarios, most commonly when urinary calculi require characterization in advance of surgical treatment. Minimization of radiation dose is essential; however, ultra-low dose, noncontrast computed tomography (CT) provides useful anatomic detail, especially information about urinary tract calcification. Both contrast-CT and magnetic resonance imaging (MRI) can provide detailed information on the vascular and urographic anatomy of the urinary tract, when required.

Endoscopic evaluation by cystourethroscopy can be combined with retrograde ureteropyelography and ureterorenoscopy to allow endoscopic and radiologic assessment of the upper urinary tracts in combination with lower tract assessment. Although it requires anesthesia in most cases, retrograde ureteropyelography avoids the nephrotoxic effect of intravenous iodinated contrast agents required for CT urogram.

6.2.3 Changes to continence with BPH

The natural history and impact of BPH on patients with congenital NGB has not been described. Anecdotally, rising leak point pressures from BPH can manifest as new-onset urinary retention (and its sequelae, infection, urinary frequency, overflow incontinence, and in advanced situations, hydronephrosis and renal compromise). Men with congenital NGB may present atypically with BPH and with manifestations more dire than in men with normal bladders. When BPH is suspected in this population, the early use of diagnostic interventions (eg, cystourethroscopy and urodynamics) is often necessary to optimize management.

6.2.3.1 Recommendation

- BPH assessment in men with congenital NGB should include a careful clinical evaluation, urine culture, flow rate, and post-void residual to assess bladder emptying for initial screening. A low threshold for urodynamic and cystoscopic evaluation of upper tract imaging is warranted to assess bladder behaviour and plan treatment.

6.2.4 Specific considerations with the management of BPH

6.2.4.1 Nonoperative management

The lack of literature relating to men with both BPH and NGB has been highlighted, but this should not stop the appropriate use of all forms of established management where they can be safely applied. In general, pharmacotherapy may involve a 5α-reductase inhibitor (5-ARI) and/or α-adrenergic antagonist (α-blocker [AB]), while intermittent catheterization remains another trusted nonoperative option.

The use of a 5-ARI to reduce prostate size may not only improve voiding[4] but also facilitate intermittent catheterization, should the prostate be enlarged to a degree that physically obstructs catheterization or results in pain with catheter passage. ABs are commonly used to improve voiding; however, while AB therapy can benefit mild to moderate obstruction in men without NGB, it may not be as useful in patients with NGB, based on an extrapolation from observations in acquired neurodegenerative conditions.[8]

If medication fails, the use of CIC is strongly preferred over an indwelling catheter due to the risks associated with indwelling catheters.[6] Overall, the use of intermittent catheterization presents an excellent option for managing BPH, as long as it can be performed in a safe manner. This is particularly true in men with atonic bladder and bladder instability who are at high risk for retention and urinary incontinence following prostate reduction surgery.

TABLE 6-1 Intermittent vs Continuous Bladder Drainage

Complication:	Continuous bladder drainage	Intermittent catherization
Infection	Infection (urethritis, cystitis, abdominal wall)	Minimized by sterile intermittent catherization
Encrustation, calculi	Catheter calculus, vesical calculus	Rare
Catheter blockage, leakage around catheter	Present	Absent
Loss of vesical tone	Contributory	Vesical tone maintained
Loss of bladder capacity, contraction	Present	Absent
Urethral and bladder trauma	Due to insertion, traction on catheter	Due to insertion
Abdominal wall trauma	May result from suprapubic insertion	Non-existent
Injury to intra-abdominal structures	May result from suprapubic insertion	Rare
Urethral stricture	More common (due to trauma, recurrent urethritis, false passage)	Rare
Sexual dysfunction	Present with urethral catheterization	Rare
Bladder cancer	Rare	Rare

Adapted from: Ramakrishnan K and Mold J. Urinary catheters: a review. *The Internet Journal of Family Practice*. 2004;3(2):1–12.

Nonoperative or conservative management should be favoured in situations where it is unclear whether symptoms stem from BPH or NGB[3,8]; there is a poor evidence base to guide treatment in either direction. Quality of life and symptom improvement need to be the principal goals of treatment.

6.2.4.2 Operative management

Similar to medical therapy, surgeons should take care to ensure a procedure does not make patients worse than they were before[6]; the risk of worsening urinary incontinence needs to be considered.[8] A systematic review noted surgery could achieve lower post-void residual bladder volumes in patients with SCI but tended not to benefit other etiologies of NGB (ie, stroke) as much.[9] Individualized management based on careful bladder evaluation, as mentioned above, is critical.

Urodynamics and cystoscopy are essential for preoperative assessment. Specifically, caution is necessary when operating on men with neuropathy at, or distal to, the sacral spinal cord, involving the pudendal nerve or other peripheral motor neurons.[6,8] Men with abnormal sphincter control in preoperative urodynamics developed unspecified urinary incontinence, whereas men with preoperative urge urinary incontinence tended to continue experiencing this postoperatively.[9]

The literature around newer, office-based BPH procedures does not address their application or risks in men with NGB. These relatively new procedures—including prostate artery embolization, prostatic urethral lift, and convective water vapour ablation—have the advantage that they can be performed in the office under local anesthesia. They offer an alternative to an endoscopic surgical procedure and a lower anesthesia risk.

The 5-years' data from a prospective analysis of the prostatic urethral lift and 3-years' results from a similar study of convective water vapour ablation demonstrate durable improvements in QoL and objective BPH outcomes.[23,24] However, in patients with NGB, other issues may present challenges to performing procedures in the office and achieving good outcomes, including limited positioning due to spinal deformity, limb contractures, or obesity.[9]

A markedly enlarged prostate may be encountered in a patient with NGB. Similar to patients without NGB, management options include simple prostatectomy and endoscopic enucleation, as delineated in the recent 2018 version of the American Urological Association guidelines on surgical management of lower urinary tract symptoms attributed to BPH.[25] Regarding simple prostatectomy, considerations such as body habitus and surgical access to the pelvis should be considered, suggesting the potential benefits of a robotic-assisted endoscopic approach versus an open approach.

6.2.4.3 Recommendations

- Nonoperative management, including medication or intermittent self-catheterization, should be considered as first line. The risks of any intervention need careful evaluation to avoid worsening a patient's symptoms, such as promoting incontinence and persistent urinary retention.

- Bladder outflow surgery should be performed after consideration of the patient's specific neurologic status and baseline bladder function (including urodynamics), and careful assessment of the patient's urinary sphincter function to inform decision making. There is not enough data to determine superiority of any specific prostate-reducing technology over another in the congenital neuropathic population.

6.3 Prostate Cancer Screening and Management

In developed countries, over the last three decades, prostate cancer has become the most common cancer diagnosed in men and one of the leading causes of cancer-related death. The advent of prostate-specific antigen (PSA) testing in the late 1980s has led to a change in disease spectrum and outcome, with a shift to earlier diagnosis and lower-stage cancer at diagnosis. Arguably, screening has resulted in better cancer outcomes and an improved understanding of the natural history of the disease, but at a cost of over diagnosing and over treating low-grade, low-risk prostate cancers.[26] However, there is also evidence that if potentially aggressive prostate cancers are diagnosed early, then the effects of metastatic progression and cancer-related mortality can be reduced.[27]

6.3.1 Risk factors for prostate cancer in patients with neuropathy

Increasing age is the main risk for prostate cancer, with adenocarcinoma rare below the age of 40 years, but increasing in incidence from the sixth decade onward. Genetics play a part, with a family history of a first-degree male relative increasing the risk for the disease. There is also a relationship between ethnic origin and risk, with African Caribbean and African American patients having a threefold increased risk for the disease and a higher likelihood of aggressive cancer when compared with white patients. Less strong relationships exist between high sex drive, diet, and lifestyle factors and a reduced prostate cancer risk.

There is very little evidence relating to the risk for prostate cancer in patients with NGB. Prostate cancer is asymptomatic in its early stages. PSA screening is offered to healthy men from their mid-40s to late 60s who have good life expectancy. It is possible, therefore, that men with a congenital abnormality are perceived as being less healthy and may be offered PSA testing less frequently than their peers.[28] There is evidence that certain groups of men with a neurological abnormality (eg, a spinal injury) present with prostate cancer at a later stage than patients without neuropathy of a similar age.[29] This is more likely to be a later diagnosis than an altered, natural history of the disease.

Baseline abnormal bladder function and other visceral effects of neuropathy could mask some symptoms of late prostate cancer. Men with locally advanced prostate cancer may present with either obstructive or irritative bladder symptoms, which could be assumed to be the effects of NGB. A small percentage also present with bowel dysfunction. Metastatic disease with bone pain or neurological sensory or motor loss could be masked by the effects of neuropathy, and as a result are missed by clinicians.

6.3.1.1 Recommendations

- The evidence suggests that neuropathy per se, or its underlying causes, does not increase the risk of men developing prostate cancer.
- Age-appropriate testing of PSA or other diagnostic modalities should be offered to patients with congenital anomalies.
- Some symptoms associated with late prostate cancer may be assumed to be part of a preexisting condition and healthcare professionals need to be aware of this.

6.3.2 Diagnostic paradigms and limitations

The diagnosis of prostate cancer is still largely driven by the use of PSA testing. If this is not offered, then later diagnosis of clinically significant prostate cancer is more likely. It is important to note that the use of PSA as a screening test has not been validated in men with NGB. There are no studies to-date that characterize "normal" PSA levels in men with chronic bacteriuria or who are using CIC. UTIs are known to increase PSA levels temporarily, and the timing after which PSA levels return to baseline following an infection is not well characterized. While PSA testing alone is already a somewhat poor screening tool for prostate cancer in men without NGB, these additional factors further diminish its value in our populations.

In recent years, the diagnostic pathway for prostate cancer has changed. A raised PSA value will more commonly trigger a multiparametric MRI (mpMRI) scan and targeted biopsy of "significant" lesions through the perineum as a preferred route. The alternative trans-rectal approach to prostate biopsies has higher UTI and urosepsis complication rates to which men with congenital urinary tract anomalies may be more vulnerable. In most men with neuropathy, this pathway should present no issues. MRI may be contraindicated in a small number of patients with implantable devices, such as sacral nerve stimulators; however, modern materials and scan technology make this less of an issue. Previous reconstruction of the urethra bladder, bladder neck, or urethra may make prostate access for biopsy more complex, but in the majority of cases, biopsy should remain achievable.

6.3.2.1 Recommendation

- Men with "normal" risk factors and/or raised PSA levels with neuropathy and reasonable life expectancy should be managed the same as patients without neuropathy of a similar age.

6.3.3 Treatment of prostate cancer

The management of prostate cancer can largely be divided into the management of localized, curable cancer and that of more advanced disease. Both may offer challenges in the complex urologic patient.

Patients with localized, low-risk prostate cancer may be offered active surveillance, with treatment only in the minority of patients who show signs of progression. The developed protocols now involve PSA testing, mpMRI, and occasional rebiopsy, which is possible in patients with neuropathy, subject to the limitations described above. Those patients deemed at higher risk for progression to metastases and death, with intermediate- to high-risk disease, will usually be offered radical prostatectomy or radiation.

Whether performed by robotic, laparoscopic, or open method, an issue with radical prostatectomy may be access. If a patient has undergone reconstruction, for example enterocystoplasty or urinary tract diversion, transperitoneal robotic or laparoscopic surgery will be more challenging due to the difficulty with port placement as a result of adhesions. However, it is feasible, and should be performed by surgeons with adequate expertise and experience in complex prostate surgery. Open surgery is usually extraperitoneal, and access will usually be straightforward, unless there has been extensive bladder neck surgery. Bladder neck surgery, either endoscopic or reconstructive, increases the difficulty of any form of radical prostatectomy. The perineal approach is still an option for radical prostatectomy if suprapubic access is impossible.

A second challenge is predicting and minimizing the side effects of radical prostatectomy in men with NGB. In non-neuropathic, radical prostatectomy patients, there is a high risk for continence issues and other bladder symptoms—many of which are short to medium term, but in a proportion of patients, issues may persist long term. In men with neuropathy affecting the bladder, these effects may be exacerbated by preexisting bladder dysfunction and sphincteric insufficiency.[30] Therefore, a careful assessment (including urodynamic investigation), cystoscopy to examine the external sphincter, and careful counselling about the likely bladder outcomes of surgery are essential in this group. If risks for incontinence are deemed high, the consideration of supravesical diversion or augmentation cystoplasty concurrent with prostatectomy may be reasonable.

Sexual function should be assessed preoperatively, as an underlying condition may have an effect on erectile or ejaculatory function. The addition of an operation that can result in erectile dysfunction needs to be considered carefully in the decision process.

External beam radiation to the prostate may result in transient radiation effects to surrounding structures, despite advances in sculpting the radiation beam to the prostate. In men, this often results in short- to medium-term irritative bladder or bowel symptoms. If there are preexisting bladder or bowel dysfunctions, the effects of radiation or any local treatments are unpredictable and may be very distressing to the patient. This also applies to sexual function. The longer-term (cumulative) impact of radiation on a neuropathic bladder is poorly described. If there has been prior reconstructive surgery, radiation to the prostate is carefully considered and may be contraindicated. Unpredictable anatomy,

presence of bowel segments and their bladder pedicles, continence issues, and small capacity bladders make administering radiotherapy difficult, with a higher risk for significant complications, such as localized ischemic necrosis.

The primary treatment for advanced or metastatic prostate cancer remains hormonal ablation, usually with luteinizing hormone-releasing hormone (LHRH) analogues to reduce androgens to castrate levels. Such treatment can result in bone loss, muscle loss, lethargy, increased cardiac events, and loss of drive and libido. Patients who are non–weight-bearing, as is common in men with neuropathic bladder, are at risk for bone demineralization, and may share other risk factors that are noted above, related to a lack of physical activity. This should be factored into the decision process and measures considered to reduce this risk, including organizing appropriate referrals to endocrinology, cardiology, and other medical subspecialists for active medical optimization.

6.3.3.1 Recommendations

- Men with neuropathic bladder who have a history of complex urologic reconstruction are eligible for active surveillance of prostate cancer using the same disease criteria as men with non-neuropathic bladder, as long as men with neuropathic bladder can undergo the repeated MRI and prostate biopsies required.

- Definitive treatment of localized prostate cancer in men with complex urologic conditions is possible, but decision making may require enhanced pretreatment evaluation.

- The treatments should be undertaken in a unit with expertise and experience, and tailored to the patient's specific condition.

- Close attention should be paid to the patient's baseline bladder and sexual function pretreatment, allowing for careful counselling and consent, as these groups have higher rates of erectile and continence issues following treatment.

6.4 Hypogonadism

6.4.1 Male reproductive health

Fertility issues in male patients with congenital genitourinary anomalies who transition from pediatric care to adult care are much less commonly addressed than bladder and bowel issues.[31] As survival to adulthood with congenital conditions becomes a "normal" expectation, the incidence of congenital genitourinary malformations has increased; this is possibly associated with the increased use of assisted reproductive technology (ART)[32] and increased maternal age.[33]

6.4.1.1 Penile and urethral abnormalities

6.4.1.1.1 Hypospadias and chordee

In adult men born with hypospadias, lower rates of paternity,[34] and higher rates of oligospermia[35] and cryptorchidism[36] are reported. However, there is currently no evidence to suggest that unrepaired, isolated anterior hypospadias is in itself a cause of subfertility. Instead, the presence of androgen receptor mutations and resultant partial androgen insensitivity—which have been found in most patients with hypospadias (even minor phenotypes)—may play a role in infertility for this population.[37] Severe proximal hypospadias, however, can severely impact ejaculatory function and sperm delivery at emission, and associated chordee—which can also exist in isolation (reported prevalence of 4%–10% of live births[38])—can exacerbate these challenges.

6.4.1.1.2 Epispadias

Among 15 patients with complete male-epispadias reconstruction, 80% reported overall satisfactory sexual intercourse, although the majority admitted to one or more problems with sexual function, including abnormal ejaculation (53%), diminished sensation (20%), and difficulty maintaining an erection (20%). One-third of patients with epispadias reconstruction had achieved pregnancy with a partner: 50% by using ART and 50% naturally.[39]

6.4.1.1.3 Posterior urethral valves

Men with a history of posterior urethral valves (PUV) and urinary continence have similar sexual activity scores compared with the general population, while men with PUV and incontinence have significantly lower overall sexual activity and lower International Index of Erectile Function scores.[40]

Ejaculatory function[41] and sperm count have been found to be normal in men with a history of PUV. Although sexual function is preserved, men with a history of PUV have increased semen viscosity, pH, and liquefaction time, as well as a dilated posterior urethra resulting in ejaculatory dysfunction.[42] Pyospermia with positive bacterial cultures are higher in men with a history of PUV and severe LUTS.[43] Libido, potency, and fertility may be affected in cases of chronic renal failure as a result of PUV, as well as in undescended testes, which is observed at a higher rate in men with a history of PUV (12%).[42] In terms of paternity rates, one case series quoted a rate of 33% for natural paternity, but in a very small patient cohort (6 patients).[44]

6.4.1.1.4 Micropenis

Congenital micropenis—defined as less than 7 cm in the erect state, less than 4 cm in the flaccid state, or less than 2.5 standard deviations below the mean stretched penile length for age—can be associated with other conditions such as exstrophy-epispadias, hypospadias, idiopathic micropenis, or a result of hypogonadism (hypogonadotropic or hypergonadotropic).

A review of outcomes in 46,XY individuals with micropenis after either medical treatment, corrective surgery (eg, chordee correction), or division of the suspensory ligament versus genitoplasty demonstrated that a majority of men are sexually active, though there was not definitive documentation of fertility, as this may depend on the underlying condition.[45]

6.4.1.1.5 Recommendations

- Semen analysis can be challenging in patients with congenital penile and urethral anomalies, but should be offered to men who are concerned about their fertility potential. Semen analysis will not necessarily correlate to the paternity ability in men with semen delivery challenges related to insufficient length or chordee. In these scenarios, intrauterine insemination (IUI) may be necessary.

- Ejaculatory dysfunction is a feature of epispadias. If the ejaculated semen contains sperm, then even small numbers can be used in ART. In cases of azoospermia, surgical sperm harvest may be an option. An appropriate pathway to use for nonobstructive azoospermia is described in the *European Association of Urology Guidelines on Male Infertility*,[46] with microdissection testicular sperm extraction (mTESE) being the gold standard technique with retrieval rates approaching 50%. Sperm from the harvest is then used for intracytoplasmic sperm injection (ICSI).

6.4.1.2 Scrotal and testicular abnormalities

6.4.1.2.1 Cryptorchidism

Cryptorchidism, the failure of one or both testes to descend into the scrotum before birth, has an incidence rate of 2.4% to 5% in newborns.[47] Many of these cryptorchid testes will descend spontaneously shortly after birth, but approximately 23% will remain undescended unless surgery is performed. Men with bilateral cryptorchidism have a six times greater risk of infertility when compared with men with unilateral cryptorchidism and the general male population. Approximately 10% of infertile men have a history of cryptorchidism and orchidopexy.[48]

Paternity has been reported as significantly more compromised in men with previous bilateral over unilateral cryptorchidism.[49] In men in whom a unilateral undescended testis was corrected before puberty, the incidence of paternity is normally at around 90% compared with 65% for those with bilateral undescended testes.[50] Nearly all patients with untreated bilateral cryptorchidism ultimately develop azoospermia; this drops to 42% after a successful bilateral orchidopexy.[51]

6.4.1.2.2 Retractile testes

Retractile testes descend with growth, and at the latest, by puberty. In adult life, men have normal testicular volumes and fertility.[52]

6.4.1.2.3 Hydrocele

Congenital hydrocele, on its own, seems to have no direct effect on later fertility.[53] This is despite a higher incidence of epididymal anomalies in patent processus vaginalis (a common finding in cryptorchidism), irrespective of testicular position.[54] In another group, however, the testicular location was observed as being associated with epididymal anomalies rather than patent processus vaginalis.[55]

6.4.1.2.4 Torsion

The incidence of testicular torsion in the young male population is 1 in 4,000, yet this only forms the main diagnosis in 0.5% of patients evaluated for infertility.[56] When men with torsion are compared with men who have other causes of monorchia (including trauma, tumour, and cryptorchidism), there are no significant differences in semen parameters.[57] Arap *et al.* found no difference in sperm counts and motility between men with torsion and healthy controls.[58] More long-term studies are needed to assess the outcomes of fertility parameters in this patient population to determine infertility frequency.

6.4.1.2.5 Prune belly syndrome

Prune belly syndrome (PBS), also known as Eagle-Barrett syndrome,[59] is characterized by a triad of symptoms: cryptorchidism, abdominal wall defects, and genitourinary defects. Infertility due to PBS is multifactorial and is probably related to undescended testes, prostatic and seminal vesicle hypoplasia, and absent and retrograde ejaculation.[60] One previous series showed all men with PBS and azoospermia had Sertoli cells only as assessed by testicular histology from biopsy, with another series finding germ cells present—but abnormal—in infants less than 1 year old.[61,62] There are no documented cases of unassisted paternity. Early orchidopexy increases testicular function and may help preserve their fertility potential. Normal live births of male infants following ICSI with spermatozoa from a man with PBS have been reported, and suggest that PBS is not transmitted to the male offspring through ICSI.[63]

6.4.1.2.6 Recommendations

- The recent European Association of Urology guidelines for pediatric urology recommend early surgical correction of undescended testes before 12 months of age, by 18 months at the latest, for preservation of fertility potential.[64]

- In PBS, there have been a few successful pregnancies reported through assisted reproduction, all using epididymal or testicular sperm extraction. Early orchidopexy may help preserve the fertility potential of testes. In cases of azoospermia, surgical sperm harvest may be an option. Early referral to infertility experts is recommended in men seeking paternity with PBS.

- The pathway for nonobstructive azoospermia is described in the European Association of Urology guidelines on male infertility, with mTESE being the gold standard technique, having retrieval rates approaching 50%. Sperm from the harvest can then be used for ICSI.

6.4.1.3 Bladder anomalies

6.4.1.3.1 Exstrophy

Amongst men with exstrophy anatomical considerations can cause anejaculation (because of the absence of a circumferential prostate and the bulbospongiosus muscle). Furthermore, bladder neck reconstruction may cause damage to the vasa or seminal vesicles. It is likely that the testes are normal at birth. Even in boys born with cloacal exstrophy, the testes of six that were removed at gender reassignment were found to be normal on microscopy.[65]

The penis after exstrophy reconstruction is documented as having a reduction in corporeal mass, with a greater girth and reduced length.[138] While 90% of men with exstrophy have experienced mild-to-moderate sexual dysfunction, many have achieved a satisfactory relationship and sexual intimacy.[66] Although the testes in men with exstrophy are generally normal, a majority of men (71%) were found to have oligoasthenoteratozoospermia, resulting in a 14% paternity rate.[66] In contrast to the above, other authors[67] have reported that men with bladder exstrophy had erectile and general sexual function comparable to the general population, although they had lower parity and a delayed start in sexual activity.

6.4.1.3.2 Recommendation

- Ejaculatory dysfunction problems may make semen analysis difficult in patients with exstrophy, including isolated epispadias. The presence of even a few sperm in the ejaculate indicates that production is occurring and that some technique for assisted conception may be possible. Failing this, percutaneous epididymal sperm aspiration (PESA) or TESE are alternatives prior to attempting ICSI: high ICSI success rates have been quoted in a small study.[68]

6.4.1.4 Genital tract anomalies

The mesonephric duct develops into the rete testis, efferent ducts, epididymis, vas deferens, seminal vesicle, and trigone of bladder. Congenital malformations of the mesonephric duct are often encountered in andrology practice. A study of 104 patients with congenital anomalies of the mesonephric duct showed a spectrum of anomalies, including agenesis of mesonephric structures from unilateral agenesis of the vas deferens, kidney, and left ureter (n=1); dysgenesis of the epididymis (n=5); cysts of the epididymis (n=47); agenesis of the vas deferens (n=48); and aplasia of the ejaculatory duct (n=3). In terms of fertility, only 31% of patients were naturally fertile, with the rest having disorders of the testes, epididymis, and seminal ducts. Bilateral disease was present in 55% of patients.[69]

6.4.1.4.1 Congenital absence of seminal vesicles

The seminal vesicles can be congenitally absent on one or both sides.[70] The incidence of unilateral agenesis of the seminal vesicle is 0.6% to 1%,[71] while the incidence of bilateral agenesis is unclear. Congenital absence of seminal vesicles (CASV) is not an independent condition. It is known that almost all congenital agenesis of the seminal vesicle occur in patients with congenital absence of the vas deferens (CAVD), or congenital vasoureteral communication.[70] While ectopia of the vas deferens into the ureter is caused by incomplete absorption of the common mesonephric duct,[70] CASV is associated with cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations and defects in the mesonephric duct.

The principles of treating an ectopic vas deferens are to prevent epididymitis and UTI, to preserve fertility, and to release the outlet obstruction.[72]

In cases of an ectopic vas deferens draining into a Müllerian cyst, open or trans-urethral strategies have been attempted, resulting in improvements in semen parameters.[73] Nowadays, assisted ART is available for patients with unreconstructable ductal obstructions. Microsurgical epididymal sperm aspiration (MESA) or testicular sperm extraction, combined with ICSI, have provided a viable treatment strategy for these patients.

6.4.1.4.2 Congenital unilateral absence of the vas deferens and renal agenesis

Congenital unilateral absence of the vas deferens (CUAVD) is rare. Men with unilateral absence of the vas deferens are usually fertile, and this condition is most commonly encountered as an incidental finding at the time of a vasectomy. Incidence is 0.06% to 1% in healthy men.[74] It has little clinical significance, in isolation, other than an associated 79% incidence of ipsilateral renal agenesis.[75] It is a rare cause of male infertility when it is associated with contralateral mesonephric duct abnormality.[76]

In one of the largest studies, comprising 21 patients with CUAVD, Mickle *et al.*[77] observed heterozygous CFTR gene mutations in 8 cases (38%). Notably, all of these 8 patients had noniatrogenic occlusion of the contralateral vas deferens at either the inguinal or pelvic level. Renal anomalies were present in 5 patients (24%: 4 ipsilateral renal agenesis, 1 ipsilateral pelvic renal ectopy), with all of them showing CFTR wild-type in genetic testing. Similarly, Schlegel *et al.*[76] described ipsilateral renal agenesis in 26% and heterozygous CFTR gene mutations in 25% of patients with CUAVD. Again, all patients with accompanying renal agenesis were negative for CFTR gene mutations, while all those with CFTR gene mutations had normal renal anatomy. Consequently, CFTR gene mutation screening is indicated in men with unilateral absence of the vas deferens and normal kidneys.

6.4.1.4.3 Congenital bilateral absence of vas deferens

Congenital bilateral absence of the vas deferens (CBAVD) is associated with CFTR gene mutations, and it was found in ~2% of men with obstructive azoospermia attending a clinic in Edinburgh, UK.[78] The incidence of CBAVD in men with obstructive azoospermia varies between different countries.

The clinical diagnosis of absent vasa is easy to miss, and all men with azoospermia should be examined to exclude CBAVD, particularly those with a semen volume less than 1.5 mL and pH less than 7.0. The most frequently found CFTR genetic mutations are F508, R117H, and W1282X, but their frequency and the presence of other mutations depend on the ethnicity of the patient.[78]

Men with CBAVD often have mild clinical stigmata of cystic fibrosis (CF), such as a history of chest infections. When a man has CBAVD, it is important to also test his partner for CFTR gene mutations. If the man is found to have a CFTR gene mutation and the female partner is found to be a carrier of CFTR mutations, the couple must consider very carefully whether to proceed with ICSI using the male's sperm, as the risk of having a child with CF or CBAVD will be 50%, depending on the type of mutations carried by the parents. If the female partner is negative for known CFTR mutations, the risk of being a carrier of unknown mutations is approximately 0.4%.

In instances of CBAVD without a mutation in the CFTR gene (10%–40%), the cause of this condition is often unknown. Some cases are associated with other structural problems of the urinary tract, including unilateral renal agenesis.[79]

6.4.1.4.4 Recommendations

- CASV is unreconstructable, but requires no treatment in the subgroup of CUAVD with a patent contralateral ductal system.

- In infertile male patients who present with CUAVD and contralateral ductal abnormalities, corrective surgical options in this subset include vasoepididymostomy, trans-urethral resection of the ejaculatory duct, and surgical sperm retrieval.

- For patients with CBAVD, surgical sperm retrieval (ie, PESA/TESE/mTESE) are the options prior to ICSI and *in vitro* fertilization (IVF), with yields up to 100%[80] and live birth rates of 48%.[81] These men should be referred to infertility experts if they express a desire for fertility.

- CFTR gene mutation screening is indicated in men with unilateral absence of the vas deferens with normal kidneys. In addition, abdominal ultrasound should be performed for men with unilateral or bilateral absence of vas deferens to assess for renal anomalies.[82]

6.4.1.5 Hormonal and other congenital disorders

6.4.1.5.1 Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders, each of which involves a deficiency of an enzyme involved in the synthesis of cortisol or aldosterone, or both.[83] A deficiency of 21-hydroxylase, resulting from mutations or deletions of *CYP21A*, is the most common form of CAH, accounting for more than 90% of cases.[84] The clinical phenotype of CAH depends on the nature and severity of the enzyme deficiency. A 21-hydroxylase deficiency in males is generally not identified in the neonatal period because the genitalia are normal.

Severe oligospermia (with sperm counts of less than 5 million/mL) has been observed in around half of men with CAH, and is associated with a raised follicle-stimulating hormone (FSH), decreased luteinizing hormone (LH), and testicular adrenal rest tumours. Testicular adrenal rest tumours are the most frequent cause of impaired fertility. Their location, adjacent to the testicular mediastinum, and their steroid-producing properties may interfere with spermatogenesis and Leydig cell function.[85] Most men will require intensification of glucocorticoid treatment and ART.[86,87] Genetic testing of the asymptomatic female partner is recommended for couples planning to have children.

6.4.1.5.2 Klinefelter's syndrome

Karyotype abnormalities are 8 times more common in men with nonobstructive azoospermia than in the general population. Of these men, 83% have Klinefelter's syndrome (KS).[88] The karyotype is 47,XXY, with no risk of transmission. Nearly all have azoospermia, with testicular biopsy showing

the presence of hyalinized seminiferous tubules with Leydig cell hyperplasia. A recent systematic review suggests that TESE or mTESE in subjects with KS results in sperm-retrieval rates of close to 50%, and paternity rates of close to 50%.[89]

Other syndromes—Kallmann syndrome, mild androgen insensitivity syndrome, and autosomal defects with severe phenotypic abnormalities—are well covered in *European Association of Urology Guidelines on Male Infertility*.[90]

6.4.1.6 Myelomeningocele and spina bifida

Sexual function in patients with SB varies widely and is largely dependent on the level of the spinal cord lesion.

In men with SB, those with intact sacral reflexes and about two-thirds of those with absent reflexes but a neurological level below L3 are likely to have normal sexual function and fertility. A few men with SB and levels up to T10 may have erections, but many erections are not associated with sexual stimulus.[140]

Infertility in males with SB appears to be a common problem. Although the number of men with SB who are married and actively attempting to father a child are poorly described, paternity rates are reported to be between 56% and 73%.[91,22] In men with higher lesions, infertility is partly attributed to poor penile sensation and severe erectile and ejaculatory dysfunction, while Sertoli-cell–only testicular histology is common and azoospermia may result.[93] In 10 males with impotence related to SB, electroejaculation (EEJ) revealed azoospermia in all patients.[94]

ART allows for the treatment of infertility among patients with myelomeningocele (MMC), similar to men with SCI. A study to assess the possibility of semen retrieval and to analyze the semen quality in men with MMC showed that only 2 of 9 participants achieved unassisted ejaculation. Penile vibratory stimulation (PVS) was unsuccessful in the remaining 7 participants, who then underwent EEJ under general anesthesia. In total, enough spermatozoa for use in intracytoplasmic-spermatozoa injection were retrieved from 5 participants (5/9). Testicular biopsies revealed spermatogenesis (and, thus, the reproductive potential) in 1 of these men (1/4). Therefore, in 6 of the 9 men with MMC, fatherhood seemed possible with modern ART, despite very poor semen quality.[95] There are no published series for this patient group of sperm-retrieval rates using mTESE (the current gold standard technique for azoospermia) or of live birth rates using ART, although there are data from men with SCI utilizing PVS or EEJ combined with ART, such as IUI or IVF with or without ICSI demonstrating a 39% to 64% pregnancy rate per cycle.[96]

Anejaculation is a particular feature in patients with MMC, and a stepwise approach from PVS to EEJ or surgical sperm retrieval should be considered. Most of our knowledge of this relies on data from patients with SCI, in which 1 out of 10 men require surgical extraction due to the failure of vibro or EEJ.[97] In the SCI group, semen attained by masturbation has higher sperm counts and motility to that which is attained by PVS or EEJ (with EEJ yielding lower results of the 2).[98] However, there have been no direct comparisons of ART outcomes with these different methods of sperm harvest. Unlike SCI, many men with MMC have an open bladder neck which may have been subjected to

surgical interventions for continence (therefore risking ejaculation) or, when left unaltered, invariably promotes retrograde ejaculation. The association of MMC and open bladder neck is the most important variable in success with natural or assisted ejaculate retrieval.

More work is needed to determine the sperm-retrieval and paternity outcomes of ART in patients with MMC. Also, patients should be counselled on the risk for neural tube defects (NTDs) in their offspring.

The reasons for the subnormal infertility are unclear. Normal testosterone production has been demonstrated in 90% of men with SB. In men with SB who are fertile and father children, the risk for NTD in the offspring is greater than in the general population.[99] This risk is present whether the affected parent is the mother or the father.

6.4.1.6.1 Recommendation

- Patients with poor semen parameters or anejaculation should be referred to an infertility specialist for evaluation for ejaculatory treatments or ART.

6.4.2 Female reproductive health

Children born with complex urogenital problems often undergo a series of surgical and medical interventions in childhood. Some interventions are necessary to prevent problems, such as hydrometrocolpos, or to improve voiding, whereas others, such as clitoridoplasty, may be regarded as cosmetic.[100] As adolescence approaches, menstrual problems may become evident. With progression into adulthood, issues related to sexual function and fertility may become apparent. Sexuality and fertility are important components of QoL, and the ability to bear children, prenatal management, or alternative options to childbearing need to be addressed during adolescent transition and early adulthood.[101]

6.4.2.1 Menstrual problems

Patients who have differences of sex development (DSD) and who are raised as females (eg, androgen insensitivity syndrome) may present in adolescence with amenorrhea.[102] Women with CAH may have menstrual irregularities, particularly if steroid replacement is insufficient, but the age at menarche does not differ from the general population.[103] In girls with CAH who have not undergone surgery, menstruation occurs through the urogenital sinus. In the more severe cases of a high confluence, where the vagina drains above the urethral sphincter, menstrual blood will be drained only during micturition. In those who underwent surgery as children, 36% needed revision surgery following puberty. For this reason, it is common practice to undertake an examination in adolescence, under anesthesia, to assess the surgical results and avoid functional problems.[104]

Girls with a cloacal exstrophy (CE) and classic bladder exstrophy-epispadias complex (BEEC) are likely to simultaneously have congenital uterovaginal anomalies,[105] which are difficult to identify in childhood as the uterus is small and often may not be appropriately imaged.[106] In BEEC, concerns tend to be related to introital stenosis, which may need a minor procedure to open the introitus, allowing

intercourse. In more complex patients, imaging of the uterus and identification of an obstruction may be performed.[107] On ultrasound or MRI, a mucous filled vagina may be identified well before the onset of menstruation and hematocolpos formation.

Older case series have suggested that about one-third of girls born with a CE will require surgery. There are a range of techniques for vaginal reconstruction to relieve menstrual obstruction. This can be technically challenging and, in cases of CE, may depend on the availability of adequate bowel. The patient must be prepared for all options, including hysterectomy if patency to the perineum cannot be achieved.[108] Similarly, in patients with BEEC, about one-fourth will require surgical removal of obstruction, amounting in some cases to a hysterectomy or a hemi-hysterectomy.[105,109,110]

6.4.2.1.1 Recommendations

- Females with DSD or congenital genital anomalies should be referred for evaluation of the urogenital sinus or vagina around the time of breast development, stage Tanner 3, as obstruction of menstrual flow often occurs at the time of menarche.

- Depending on the patient's condition and extent of surgery in childhood, this assessment may require imaging only or may be done alongside examination under anesthetic, with corrective measures taken as required.

6.4.2.2 Pelvic organ prolapse

Uterine prolapse—a condition usually identified in multiparous, menopausal women—is a well-recognized complication in patients with BEEC. An 18% risk for uterine prolapse has been reported in young, nonparous women with BEEC[111]; however, this rises to 30% and 50% in older and particularly parous individuals with BEEC.[109,112,113] Uterine prolapse causes bothersome symptoms, can interfere with tampon use and sexual intercourse, and thus affects QoL.[109,114] Furthermore, usual methods to treat vaginal prolapse are hindered by an altered anatomy and abdominal adhesions that are usually present due to previous reconstructive surgery. Conservative measures, such as pessary use, are unlikely to be successful and are usually only proposed as an interim solution while awaiting surgical correction or during pregnancy.[113] Although osteotomy at the primary closure of the bladder during infancy was intuitively thought to reduce the risk for uterine prolapse in later life, this has not been borne out in the literature.[112] Similarly, introitoplasty has been identified as a risk factor; however, it is more likely to readily expose a prolapse, rather than be the actual cause for it.[113]

In other patient groups, vaginal prolapse has been described as a complication of vaginoplasty, particularly when the bowel has been used as lining for the neovagina.[115-117] Bowel vaginoplasty, however, is required for a minority of patients with isolated uterovaginal aplasia or DSD, as other methods—such as vaginal dilation, the Vecchietti or Davydov procedure, and more recently buccal mucosal graft vaginoplasty—are less invasive and may be equally effective for vaginal formation.[118] Vaginal prolapse, albeit rare, has been described in women who have undergone only vaginal dilation for the creation of a neovagina. Treatment can be achieved through sacrospinous fixation or laparoscopic sacrocolpopexy.[119,120]

6.4.2.2.1 Recommendation

- Pelvic organ prolapse occurs more frequently in females with SB, BEEC, and other conditions that involve vaginal reconstruction in early life. Treatments often are more complicated in women with congenital abnormalities than in women without, and should be undertaken by providers with extensive expertise in the management of complex prolapses.

6.4.2.3 Cosmetic genital results

Women with complex, congenital urogenital anomalies may undergo surgical genitoplasty: some procedures are aimed at improving function and some are more cosmetic. Nevertheless, women with DSD will often rate the appearance of their genitalia as satisfactory, at most, and usually have more pessimistic evaluations of genital cosmesis than gynaecologists.[121] The age at first genital surgery and number of repeat surgeries, as well as degree of virilization,[122,123] appear to affect the level of satisfaction with genital appearance during adolescence and adulthood in women with CAH and other DSDs. Older cohort studies reported worse cosmetic outcomes than more recent cohort studies, with 41% of women reporting poor results, while outcomes of genital surgery tended to be somehow better in women with cloacal anomalies than in women with CAH or other DSDs.[124] More recent cohorts identify a more successful cosmetic result, at least in women with CAH, with only 14% having their genital cosmetic appearance assessed as "poor."[125] In an assessment of 26 women with BEEC, the vagina was perceived as more or less normal in 35%, with 46% believing that a sexual partner would be able to note the difference from the vaginas of other women.[114] Although recent cohorts of women with BEEC have undergone treatment strategies with improved attention to cosmesis, 40% are unhappy with the cosmetic appearance of their genitals in the long term.

The timings and technique associated with genital surgery for females born with genital anomalies is much debated due, in part, to the small numbers and great heterogeneity of the population, and also, in part, to nonstandardized follow-up of these females as they progress into adult life. All decisions should be made within a multidisciplinary team and within the framework of local regulation. At the time of writing, this area is fast changing and those participating in this work need to be apprised of the current literature at all times. Parents of children born with a genital anomaly are often included in the decision-making process, tending to opt for earlier surgery under current management principles, which do not usually offer an alternative of much support to the patient and her family.

6.4.2.3.1 Recommendation

- The timing and approach to genital revision surgery in females with genital anomalies should be multidisciplinary, include parents and, when developmentally appropriate, the child, and incorporate local and national regulations, and best practices.

6.4.2.4 Sexual function

Interlinked with the cosmetic results of genital surgery are its long-term effects on female sexual function. This relates to the ability to have penetrative vaginal intercourse and achieve orgasm, both of which are affected by scarring, stenosis, a short or inappropriately positioned vagina, and nerve damage. Beyond objectively assessed parameters, however, sexual gratification is often affected by general well-being, as well as decreased self-esteem and body image satisfaction. Data from European and American cohorts show that 10% to 48% of adult women with CAH and other DSDs have never

engaged in sexual activity, with numbers usually significantly lower than seen in the general population. There is also a tendency toward a later age of coitarche.[122,123,126-130] For those women with CAH who are sexually active, dyspareunia is a recurring complaint, as is a decreased ability for orgasm. These parameters tend to be lower in women who have undergone genital surgery and correlate with the degree of virilization at birth.[122,126,128] Objective measurements of clitoral sensitivity have demonstrated a marked deterrence in the threshold for warm, cold, and vibratory sensations in the subgroup that underwent corrective genital surgery compared to women with CAH without corrective surgery and healthy controls.[126,129]

Sexual function is also affected in women with BEEC, due to genital anatomic anomalies. These women often present with a congenital narrowing of the introitus, the clitoris usually lacks a hood and is bifid, and labia are laterally displaced. Some patients may have undergone clitoroplasty and labiaplasty procedures for cosmesis, and about four out of five will require a more minor vaginoplasty prior to being sexually active. Pelvic organ prolapses and urinary incontinence may also further interfere with sexuality. Despite this, in a recent cohort, the number of adult women with BEEC having ever been sexually active was 89%. Intercourse frequency and satisfaction, however, were affected, and scores in all sexual function domains of the Female Sexual Function Index were statistically significantly lower when compared to normative data.[114] Often the level of sexual satisfaction does not relate to the degree of genital anomaly. Psychological support appears to be an important compound that will enhance how patients perceive their genital appearance and how they will interact with a partner. Vaginismus related to pain often compounds sexual dysfunction, and involvement of pelvic physiotherapists may prove helpful in facilitating pain-free intercourse.

6.4.2.4.1 Recommendations

- Sexual problems are common in women with complex congenital genital anomalies; however, the underlying causes are multifaceted. Healthcare teams should ensure females have an anatomically adequate vagina that allows for intercourse without discomfort, where possible. Psychosexual support should be at hand as part of a multidisciplinary team, incorporating a urologist, gynecologist, pelvic PT, and psychologist to improve long-term satisfaction.

- Conservative measures, such as vaginal dilation, should be considered prior to, or in conjunction with, surgical vaginoplasty.

6.4.2.5 Fertility

Women with complex urogenital problems face a number of potential challenges, including anatomic anomalies, a potential impact on sexual function, and difficulties with becoming pregnant due to anatomical or endocrinological factors that may restrict fertility.

In women with BEEC, data show a delay in conception, with only 21% of women achieving a pregnancy within one year, as opposed to approximately 90% of the general population. It is speculated that tubal obstruction or endometriosis (resulting from adhesions secondary to prior abdominal operations) and uterovaginal anomalies may contribute to this.[131]

In women with CAH on insufficient steroid replacement, anovulation may ensue. Furthermore, increased adrenal progesterone production, even in the face of adequate CAH control, makes the endometrium less able to support embryo implantation. Although reported pregnancies in women with CAH appear to be reduced, a study by Casteras *et al.* demonstrated that within the remit of a multidisciplinary setting, adequate follicular phase, and progesterone suppression, a pregnancy can be achieved in most women with no further fertility treatment. Despite improved fecundity, however, fertility rates were 0.25 per woman, as opposed to 1.8 in the UK population.[132]

6.4.2.5.1 Recommendation

- Females with congenital abnormalities are at risk for delayed conception when faced with a variety of anatomical, endocrine, and post-surgical issues. Appropriate referral to fertility specialists is warranted in women seeking fertility.

6.4.2.6 Pregnancy outcomes and complications

Women with complex urogenital anomalies need to be followed-up within a tertiary antenatal care setting with expertise in the management of high-risk pregnancies. Uterine prolapse is commonly seen in pregnant women with BEEC, reported as high as 52%. Usually, this is treated with bed rest and a ring pessary insertion.[131] Whilst, historically, surgical repair during pregnancy has been reported, the risk to a fetus is so significant that it is not an approach that can be justified.[111] Impaired renal function prior to pregnancy increases the risk for pregnancy-induced hypertension and preeclampsia, which has been reported in 32% of patients. An abnormal placenta affects between 3.3% and 4.5% of women with placental accreta (or occasionally, percreta), becoming an increased risk in multiparous women who have had a previous cesarean section.[131,133]

Urinary infections due to obstruction or urinary stasis affect between 30% and 63% of patients. Hydronephrosis, requiring a percutaneous nephrostomy or a ureteral stent, is a common complication and has occurred in all twin pregnancies reported.[111,131,133] Patients need regular urologic monitoring, with ultrasound, and clinical reviews throughout pregnancy.

With regards to antenatal outcomes, preterm delivery is reported in about one in five patients. Elective cesarean sections are favoured in women with prior bladder neck repair and a pelvic anatomy that precludes vaginal deliveries or predisposes the fetus to malpresentation. Emergency cesarean sections should be avoided at all costs, as the anatomy following reconstruction and surgical adhesions may make access to the uterus difficult. Data have shown that the absence of appropriate support (ie, an experienced high-risk obstetrician and reconstructive urologist) increases the risk to the fetus and mother. A lower-segment cesarean section is feasible in many circumstances and is associated with a lower risk for spontaneous uterine rupture in future pregnancies.[131]

Women with CAH should remain under careful endocrine supervision and on steroid replacement during pregnancy. Doses of glucocorticoids may need to be increased for some patients; however, monitoring CAH control by measuring 17-OH-progesterone is of no value, as 17-OH-progesterone is produced by the corpus luteum and the placenta during pregnancy. Instead, CAH control should be based on clinical assessment and sequential measurement of androgens and electrolytes.[134] This management should be directed by endocrinologists and high-risk obstetricians. The rate of

gestational diabetes may increase, with some studies reporting a 20% risk,[135] whereas pregnancy-induced hypertension seems to depend on glucocorticoid dosing, with higher replacement leading to an increased risk.[136] As for other groups of women who have had reconstructive urogenital surgery, elective cesarean section may be recommended—ultimately, this is an obstetric decision, in consultation with the endocrine and urology teams. Stress-dose glucocorticoid cover should be administered peripartum and gradually tapered to previous delivery doses.[134]

6.4.2.6.1 Recommendations

- Females with complex urogenital abnormalities need shared care throughout pregnancy, involving high-risk obstetrics, urology, and other specialties as required.

- Urinary obstruction, stasis, and infections are more prevalent and significant in these patients; they need regular urologic reviews and ultrasounds throughout pregnancy.

- Elective, lower segment cesarean section is recommended in females who have had previous urogenital reconstructive surgery. Emergency cesarean section is associated with high maternal morbidity and neonatal mortality and should be avoided.

6.4.2.7 Menopause

Menopause and perimenopause have been poorly reported in women with complex congenital urogenital anomalies. This is mostly relating to the fact that successful medical and surgical treatment, since the 1950s and 1960s, has generally allowed these women to survive. The little that is known comes from studies of patients that may include older women in the cohort.

Perimenopause is often associated with anovulatory cycles and abnormal uterine bleeding, which may further impact the QoL of these women. After menopause, hypoestrogenism gradually leads to urogenital atrophy that may further impact vaginal stenosis and lead to dyspareunia.[139]

6.5 Conclusion

Most of the medical evidence on congenital urogenital anomalies comes from the pediatric population, with long-term outcomes emerging mostly over the past 15 to 20 years. As patients age, information on later phases in their lives expands. With it, more data are available to assess the long-term effects of procedures—usually performed in infancy—on reproductive health and QoL.[137]

6.6 Summary of Recommendations

6.2.3.1 Recommendation for changes to continence with BPH

- BPH assessment in men with congenital NGB should include a careful clinical evaluation, urine culture, flow rate, and post-void residual to assess bladder emptying for initial screening. A low threshold for urodynamic and cystoscopic evaluation of upper tract imaging is warranted to assess bladder behaviour and plan treatment.

6.2.4.3 Recommendations for operative management

- Nonoperative management, including medication or intermittent self-catheterization, should be considered as first line. The risks of any intervention need careful evaluation to avoid worsening a patient's symptoms, such as promoting incontinence and persistent urinary retention.

- Bladder outflow surgery should be performed after consideration of the patient's specific neurologic status and baseline bladder function (including urodynamics), and careful assessment of the patient's urinary sphincter function to inform decision making. There is not enough data to determine superiority of any specific prostate-reducing technology over another in the congenital neuropathic population.

6.3.1.1 Recommendations for risk factors for prostate cancer in neuropathic patients

- The evidence suggests that neuropathy per se, or its underlying causes, does not increase the risk of men developing prostate cancer.

- Age-appropriate testing of PSA or other diagnostic modalities should be offered to patients with congenital anomalies.

- Some symptoms associated with late prostate cancer may be assumed to be part of a preexisting condition and healthcare professionals need to be aware of this.

6.3.2.1 Recommendation for diagnostic paradigms and limitations

- Men with "normal" risk factors and/or raised PSA levels with neuropathy and reasonable life expectancy should be managed the same as patients without neuropathy of a similar age.

6.3.3.1 Recommendations for treatment of prostate cancer

- Men with neuropathic bladders who have a history of complex urologic reconstruction are eligible for active surveillance of prostate cancer using the same disease criteria as men with non-neuropathic bladder, as long as men with neuropathic bladder can undergo the repeated MRI and prostate biopsies required.

- Definitive treatment of localized prostate cancer in men with complex urologic conditions is possible, but decision making may require enhanced pretreatment evaluation.

- The treatments should be undertaken in a unit with expertise and experience, and tailored to the patient's specific condition.

- Close attention should be paid to the patient's baseline bladder and sexual function pretreatment, allowing for careful counselling and consent, as these groups have higher rates of erectile and continence issues following treatment.

6.4.1.1.5 Recommendations for penile and urethral abnormalities

- Semen analysis can be challenging in patients with congenital penile and urethral anomalies, but should be offered to men who are concerned about their fertility potential. Semen analysis will not necessarily correlate to the paternity ability in men with semen delivery challenges related to insufficient length or chordee. In these scenarios, intrauterine insemination (IUI) may be necessary.

- Ejaculatory dysfunction is a feature of epispadias. If the ejaculated semen contains sperm, then even small numbers can be used in ART. In cases of azoospermia, surgical sperm harvest may be an option. An appropriate pathway to use for nonobstructive azoospermia is described in the European Association of Urology Guidelines on Male Infertility, with microdissection testicular sperm extraction (mTESE) being the gold standard technique with retrieval rates approaching 50%. Sperm from the harvest is then used for intracytoplasmic sperm injection (ICSI).

6.4.1.2.6 Recommendations for scrotal and testicular abnormalities

- The recent European Association of Urology guidelines for pediatric urology recommend early surgical correction of undescended testes before 12 months of age, by 18 months at the latest, for preservation of fertility potential.

- In PBS, there have been a few successful pregnancies reported through assisted reproduction, all using epididymal or testicular sperm extraction. Early orchidopexy may help preserve the fertility potential of testes. In cases of azoospermia, surgical sperm harvest may be an option. Early referral to infertility experts is recommended in men seeking paternity with PBS.

- The pathway for nonobstructive azoospermia is described in the European Association of Urology guidelines on male infertility, with mTESE being the gold standard technique, having retrieval rates approaching 50%. Sperm from the harvest can then be used for ICSI.

6.4.1.3.2 Recommendation for bladder anomalies

- Ejaculatory dysfunction problems may make semen analysis difficult in patients with exstrophy, including isolated epispadias. The presence of even a few sperm in the ejaculate indicates that production is occurring, and that some technique for assisted conception may be possible. Failing this, percutaneous epididymal sperm aspiration (PESA) or TESE are alternatives prior to attempting ICSI: high ICSI success rates have been quoted in a small study.[84]

6.4.1.4.4 Recommendations for genital tract anomalies

- CASV is unreconstructable, but requires no treatment in the subgroup of CUAVD with a patent contralateral ductal system.

- In infertile male patients who present with CUAVD and contralateral ductal abnormalities, corrective surgical options in this subset include vasoepididymostomy, trans-urethral resection of the ejaculatory duct, and surgical sperm retrieval.

- For patients with CBAVD, surgical sperm retrieval (ie, PESA/TESE/mTESE) are the options prior to ICSI and *in vitro* fertilization (IVF), with yields up to 100%[100] and live birth rates of 48%.[101] These men should be referred to infertility experts if they express a desire for fertility.

- CFTR gene mutation screening is indicated in men with unilateral absence of the vas deferens with normal kidneys. In addition, abdominal ultrasound should be performed for men with unilateral or bilateral absence of vas deferens to assess for renal anomalies.[102]

6.4.1.6.1 Recommendation for myelomeningocele and spina bifida

- Patients with poor semen parameters or anejaculation should be referred to an infertility specialist for evaluation for ejaculatory treatments or ART.

6.4.2.1.1 Recommendations for menstrual problems

- Females with DSD or congenital genital anomalies should be referred for evaluation of the urogenital sinus or vagina around the time of breast development, stage Tanner 3, as obstruction of menstrual flow often occurs at the time of menarche.

- Depending on the patient's condition and extent of surgery in childhood, this assessment may require imaging only or may be done alongside examination under anesthetic, with corrective measures taken as required.

6.4.2.2.1 Recommendation for pelvic organ prolapse

- Pelvic organ prolapse occurs more frequently in females with SB, BEEC, and other conditions that involve vaginal reconstruction in early life. Treatments often are more complicated in women with congenital abnormalities than in women without, and should be undertaken by providers with extensive expertise in the management of complex prolapses.

6.4.2.3.1 Recommendation for cosmetic genital results

- The timing and approach to genital revision surgery in females with genital anomalies should be multidisciplinary, include parents and, when developmentally appropriate, the child, and incorporate local and national regulations, and best practices.

6.4.2.4.1 Recommendations for sexual function

- Sexual problems are common in women with complex congenital genital anomalies; however, the underlying causes are multifaceted. Healthcare teams should ensure females have an anatomically adequate vagina that allows for intercourse without discomfort, where possible. Psychosexual support should be at hand as part of a multidisciplinary team, incorporating a urologist, gynecologist, pelvic PT, and psychologist to improve long-term satisfaction.

- Conservative measures, such as vaginal dilation, should be considered prior to, or in conjunction with, surgical vaginoplasty.

6.4.2.5.1 Recommendation for fertility

- Females with congenital abnormalities are at risk for delayed conception when faced with a variety of anatomical, endocrine, and post-surgical issues. Appropriate referral to fertility specialists is warranted in women seeking fertility.

6.4.2.6.1 Recommendations for pregnancy outcomes and complications

- Females with complex urogenital abnormalities need shared care throughout pregnancy, involving high-risk obstetrics, urology, and other specialties as required.
- Urinary obstruction, stasis, and infections are more prevalent and significant in these patients; they need regular urologic reviews and ultrasounds throughout pregnancy.
- Elective, lower segment cesarean section is recommended in females who have had previous urogenital reconstructive surgery. Emergency cesarean section is associated with high maternal morbidity and neonatal mortality and should be avoided.

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CONGENITAL LIFELONG UROLOGY: A JOINT SIU-ICUD INTERNATIONAL CONSULTATION

Until fairly recently, urological care has been divided into pediatric and adult services. As such, many patients born with urologic diseases have fallen under the purview of the pediatric urological care model. As treatments have improved, so has longevity for these patients, with most living to adult life with high expectation for quality of life, sexual function and fertility. Without expertise in congenital conditions and their often complex treatments, adult urological providers are often ill-prepared to provide even basic urological care to this population.

The 2018 Société Internationale d'Urologie - International Consultation on Urological Diseases (SIU-IUCD) Joint Consultation on *Congenital Lifelong Urology* aims to shed light on the specific needs of patients with congenital urological diseases as they progress into adult life. The consultation brought together experts in both pediatric and adult care, with expertise in neurourology, genitourinary reconstruction, fertility, transplant and endourology from across the globe. While impossible to comprehensively cover every aspect of congenital urology in a single text, this book presents best practice and general guidelines for treatment and care for the most commonly encountered urological problems faced in adulthood for patients born with congenital urological diseases.

We hope that you will find it an essential reference when caring for patients in your practice with unique congenital challenges.

Dan Wood and Hadley M. Wood
Chairs, SIU- ICUD Joint Consultation on Congenital Lifelong Urology:
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