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Current management of classic bladder exstrophy in the modern era

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Abstract

Background Classic bladder exstrophy is a complex, multi-system congenital malformation affecting formation of the genitourinary system, pelvis, and abdominal wall.

Main body Historically children with this abnormality were consigned to poor outcomes and quality of life. Modern advancements in the diagnosis and management of this disorder have resulted in low mortality rates and shifted clinical focus toward optimizing quality of life.

Conclusion Modern techniques in addition to recent discoveries in the diagnosis and delayed management of this disorder have enabled high rates of urinary continence, genital cosmesis, and an improved quality of life. This is an updated overview of the pathology, diagnosis, and management of this rare disorder.

Keywords Bladder exstrophy, Transitional urology, Congenitalism

1 Background

The bladder exstrophy-epispadias complex (BEEC) is a rare spectrum of defects affecting the genitourinary and gastrointestinal tracts, musculoskeletal system, pelvic floor musculature, and bony pelvis. The BEEC spectrum ranges from mild isolated epispadias, presenting with a dorsally open urethral meatus, mild pubic diastasis, and closed abdominal wall and bladder. In contrast, the most severe form of cloacal exstrophy, or OEIS (omphalocele, exstrophy, imperforate anus, and spinal abnormalities) syndrome, consists of debilitating multisystemic anomalies of the genitourinary, musculoskeletal, and gastrointestinal systems. The most common presentation of BEEC, classic bladder exstrophy (CBE) presents with a wide pubic diastasis, abdominal wall defect exposing an open bladder and urethra with an epispadias opening.

Surgical management of CBE requires multiple reconstructive surgeries starting with closure of the bony pelvis, bladder, and anterior abdominal wall, followed later by epispadias repair. Recent trends have shifted management toward scheduled delayed closure in the 6-8th week of life and utilization of pelvic osteotomy and lower extremity immobilization to ensure complete approximation and sufficient deepening of the pelvis for anatomic placement of the bladder. While current techniques achieve reasonable success in preservation of renal function, continence, and cosmesis, there are still discoveries that are needed to improve quality of life even more.

2 Epidemiology

Within the USA, the incidence of bladder exstrophy is estimated to be 2.15 cases per 100,000 live births [1, 2]. In a broader international population, Cervellione et al. reported an incidence of 1 in 46,000 live births [3]. Most recently, an increased live prevalence of CBE was reported amidst the German population at 1 in 30,675 live births [4]. Historically, CBE is most common among boys with a male-to-female ratio ranging between 2–5: 1 [5–7].

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Risk factors include Caucasian race, young maternal age, advanced paternal age, maternal multiparity, and use of assisted-reproductive technologies (i.e., in vitro fertilization) [1, 8, 9]. In relevant studies, no meaningful associations have been made between CBE incidence and periconception maternal exposure to alcohol, drugs, radiation, or infections [10]. The risk of bladder exstrophy in the offspring of individuals with bladder exstrophy is approximately 500-times greater, 1 in 70 births, than baseline risk in the general population [5].

3 Etiopathogenesis

While the granular causes of BEEC are not completely understood, the predominately held theory popularized by *Marshall and Muecke* traces the basic defect to an abnormal overdevelopment of the cloacal membrane in the fourth week of gestation [11]. The cloacal membrane is a bilaminar layer situated at the caudal end of the germinal disk which occupies the infraumbilical abdominal wall. The overdevelopment of the cloacal membrane prevents mesenchymal migration between the ectoderm and endoderm. The effect of this overdevelopment causes (1) limited development of lower abdominal musculature and pelvic bones and (2) a propensity for early rupture of the cloacal membrane due to innate instability. The timing and location of rupture of the cloacal membrane are thought to dictate the patient's presentation along the Bladder Exstrophy-Epispadias spectrum [12, 13]. Epispadias occurs if the rupture produces a division or nonunion at the distal end of the urinary tract. CBE results if the rupture occurs after the urorectal septum which divides the gastrointestinal from the genitourinary tracts while CE (cloacal exstrophy) results if the rupture occurs before this separation [14].

While several genetic studies are underway, the majority of BEEC cases are sporadic without Mendelian inheritance. Some evidence suggests an association between CBE and the CASPR3 gene, p63 tumor suppressor gene, and 22q11.2 duplications [9, 15–17]. The p63 gene, a member of the p53 tumor suppressor gene family, may have the strongest association with CBE as it is highly expressed within the bladder and overlying skin [18]. Animal studies consisting of p63 knockout in mice resulted in CBE-like anomalies [19, 20].

4 Anatomic considerations

4.1 Urogenital anomalies

In CBE, the bladder and posterior urethra are exposed anteriorly through a triangular abdominal defect. Histologically, the bladder appears immature as demonstrated by significantly reduced myelinated nerves [21]. Further, the exstrophied bladder presents with an increased ratio of collagen to smooth muscle compared to normal controls and may correct following a successful closure [22–25]. Historically, neonatal closures of the bladder soon after birth were the standard of care except in cases where delayed closure were necessary. Delayed closure was indicated whenever hamartomatous polyps are present on the bladder mucosa, a bladder template <3 cm in diameter, fibrosis of the bladder template, or patient referral is delayed [26]. In the modern era, scheduled delayed closure for patients has become the new standard of care even for patients who could be candidates for neonatal closure.

Sufficient bladder growth for continent bladder neck reconstruction occurs in approximately 60% of successfully closed CBE patients [27]. If bladder growth does not reach sufficient capacity, a bladder augmentation cystoplasty may be required [28]. In a subset of patients with extremely small or excessively fibrotic bladders, cystectomy with urinary diversion (continent catheterizable pouch or orthotopic neobladder) is favored over augmentation [29, 30].

The upper urinary tract is generally normal at birth, but anomalies do occur. Approximately 3% of patients will have an associated renal anomaly (duplicated system, solitary kidney, ureteropelvic junction obstruction, etc.) [31, 32]. The entry course of the ureteral section terminating into the bladder predispose all CBE patients to vesicoureteral reflux following bladder closure [33, 34]. If the reflux does not cause upper tract changes, patients can be managed conservatively until reimplantation can be paired with continence surgeries.

In the male CBE patient, the phallus is shorter and wider than normal controls with the open urethral plate on the dorsal surface. Most cases will also present with significant dorsal chordee. The short and broad phallus is influenced by pubic diastasis and the lateralization of corporal bodies [35].

In the female CBE patient, the dorsal urethra remains open at the distal aspect creating a patulous bladder neck. The vagina and introitus are displaced anteriorly with a flattened and lateralized mons pubis. Female CBE frequently presents with a bifid clitoris located in the anterior vaginal wall surrounded with divergent labia. The vagina is shallow and stenotic [36]. Mullerian anomalies are more commonly associated with the more severe cloacal exstrophy condition but have been reported with CBE patients [37, 38].

4.2 Bony pelvis and spinal defects

Among CBE patients, the bony pelvis presents with a characteristic widening of the pubic symphysis (pubic diastasis), rotational, and dimensional anomalies [39]. Pubic diastasis is secondary to malrotation of the innominate bones which evert, or externally rotate, the pubic rami at their junction with the iliac bones. Classic bladder exstrophy patients have an average pubic diastasis between 4 and 5 cm [39, 40]. Additional rotational anomalies include external rotation

of the anterior pelvic segment, coronal rotation of the sacroiliac joint, acetabular retroversion, convergence of iliac wings, and femoral retroversion. The bony pelvis of the CBE patient has a 30% shortened anterior pubic segment and increased intertriradiate cartilage distance [39]. The summation of these bony anomalies increases distance between the hips and accounts for waddling gait and outward rotation of lower limbs in children with CBE. The functional outcomes derived from the bony pelvis cause minimal disability and will self-correct to a small degree overtime [41].

Spinal anomalies are relatively uncommon among patients with classic bladder exstrophy. In a popularized 1997 study of 299 CBE patients from a single institution, the rate of spinal anomalies, excluding normal variants, was found to be 6.7% [42]. Spinal anomalies consisted of uncomplicated scoliosis (2.7%) and spinal dysraphism (4%). In addition to spinal anomalies, 11% of patients presented with normal variants (e.g., spina bifida occulta, lumbarization, sacralization). A single patient with myelomeningocele suffered clinical neurological dysfunction (0.3%).

4.3 Pelvic floor defects

Preoperative magnetic resonance imaging (MRI) among CBE patients reveals several key characteristics of anomalous development. In general, the preoperative CBE pelvic floor consists of a posteriorly positioned, irregularly shaped levator ani and flattened puborectal sling. As a result of these changes, the puborectal slings support twice as much body cavity area than normal [41]. According to most recent literature, the severity of pubic diastasis does not account for the disproportionate curvature of the pelvic floor [43]. The aforementioned abnormalities contribute to incontinence and predispose females to complications including uterine prolapse [44]. Using 3D MRI to compare the pelvic floor of pre- and post-repair CBE patients, Stec et al. discovered closure (1) reshapes pelvis from a boxlike configuration to a more inwardly rotated hammock; (2) redistributes a significant portion of the levator group into the anterior compartment; and (3) facilitates smooth uniform contouring of the pelvic floor [45].

4.4 Abdominal wall anomalies

Classic bladder exstrophy is associated with a triangular abdominal wall and fascial defect limited superiorly by the umbilicus and inferiorly by the intrasymphyseal band [41]. Occupying the defect is the exstrophied bladder and posterior urethra. Inferiorly the intrasymphyseal band is tethered between the posterior vesicourethral unit and the pubic ramus. Concurrent umbilical hernias are a common, but generally insignificant, finding and may be repaired at time of primary closure. Indirect inguinal hernias are similarly common as a result of a persistent processus vaginalis, large inguinal rings, and linear orientation of the inguinal canal.

4.5 Anorectal defects

Misalignment of the anal canal is a common finding among classic bladder exstrophy patients. The anterior displacement of the anus and anal sphincter, in combination with pelvic floor anomalies, predisposes patients to fecal incontinence. On occasion, CBE patients may present with concurrent omphalocele, imperforate anus, rectal stenosis, and/or rectal prolapse [46]. However, incidence of major gastrointestinal anomalies is more commonly associated with cloacal exstrophy. Anal continence is expectedly imperfect at early ages and improves with time and successful primary closure. Rectal prolapse is frequently found among older untreated CBE children but is often easily reduced. In the case of rectal prolapse following successful primary closure, clinicians should maintain a high suspicion for bladder outlet obstruction and low threshold to evaluate patients by cystoscopy [47].

4.6 Complex variants

Variants of CBE include skin covered bladder exstrophy, duplicated bladders, superior vesical fistulas, and epispadias with major bladder prolapse [48]. Skin-covered exstrophy presents with the bladder directly beneath an infraumbilical bulge of intact skin with laterally displaced rectus muscles. Duplicated bladders may present as either anterior–posterior or side-to-side. An anterior–posterior duplication may present with a patch of exstrophic mucosa on the infraumbilical aspect of the abdomen. The superior vesical fistula presents as an abdominal wall defect communicating with the urinary bladder.

5 Prenatal diagnosis

Reports on the rate of prenatal diagnosis of classic bladder exstrophy range somewhere between 12.5 and 75% [49–53]. Since the turn of the century, the rate has been approximately 47% and increasing [54]. The hallmark findings for prenatal diagnosis include: (1) absence of bladder filling, (2) a low-set umbilicus, (3) widening pubic ramus, (4) diminutive genitalia, and (5) lower abdominal mass [55]. The diagnosis is often missed or misdiagnosed as omphalocele or gastroschisis. Inability to identify bladder filling in two consecutive ultrasounds 90 min apart and/or a pubic diastasis ≥ 1 cm at ≥ 20 weeks gestation should merit referral to an experienced exstrophy center for evaluation [55, 56]. Existing online health information regarding exstrophy may be incomprehensible for most caregivers, making early prenatal consultation crucial [57]. Prenatal consultation allows confirmatory imaging and the opportunity for family members to receive education on the prognosis of bladder exstrophy, meet members of the multidisciplinary exstrophy team, tour intensive care units, and connect with other bladder exstrophy families [54, 58, 59].

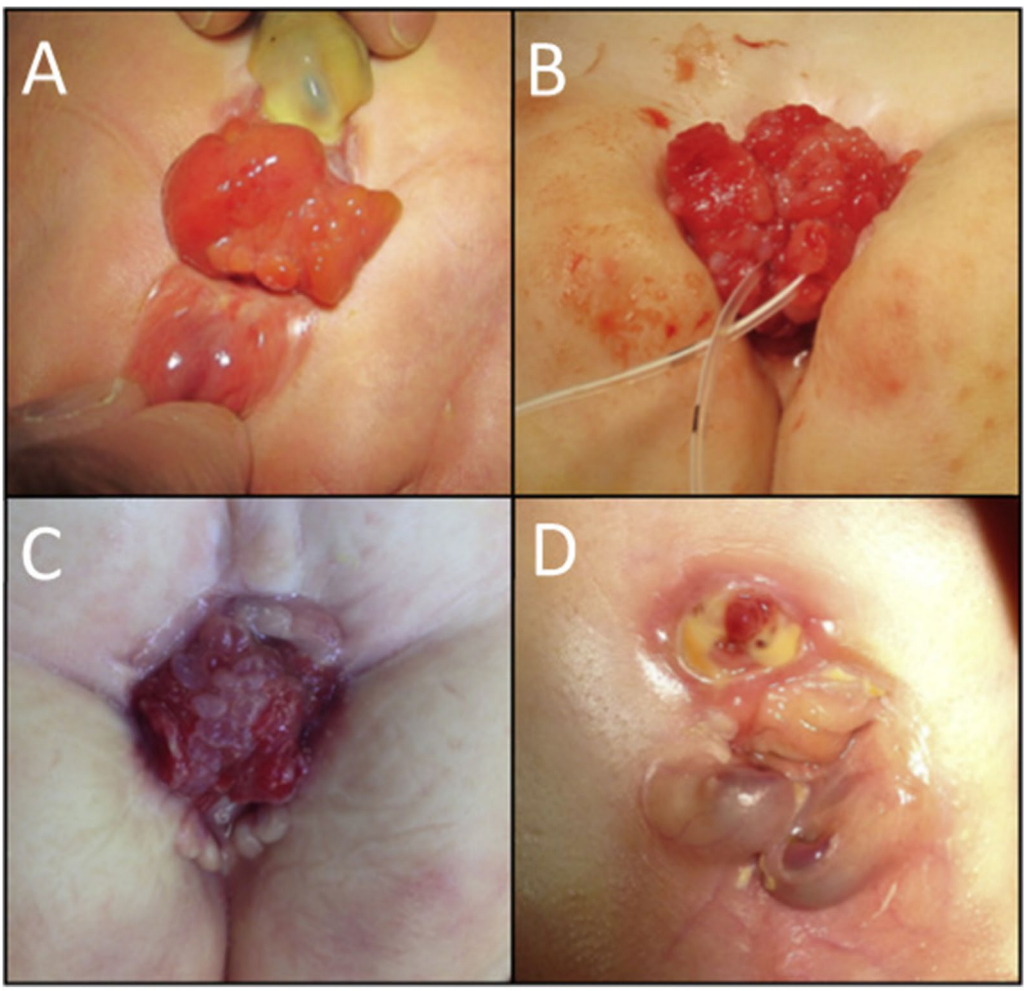
6 Evaluation and management at birth

6.1 Selection of patients for immediate closure

At birth, careful assessment and consideration of the exstrophy patient must be undertaken by an experienced exstrophy surgeon and a pediatric orthopedic surgeon. Examination under anesthesia may yield previously unappreciated bladder and should be considered [41, 60]. If the infant possesses a large, elastic bladder template, free of any polyps, and under the care of an experienced exstrophy team, then, a newborn closure may be considered. Some proponents of early closure claim that a rapid closure allows for early bladder cycling and a resultant larger capacity [61].

6.2 The inadequate bladder template and elective delayed closure

A small, fibrotic bladder or one with hamartomatous polyps is unsuitable for newborn closure and further assessment under anesthesia by an experienced exstrophy surgeon should be made [60, 62]. Other conditions that may forestall neonatal closure include ectopic bowel within the bladder, penoscrotal duplication, and significant bilateral hydronephrosis. In Baradaran et al., study of delayed primary closures, the authors compared bladder capacity in delayed closure patients due to inadequate templates with those due to late referrals [63]. They concluded that although the total measured capacity of delayed closure was reduced, the annual growth rate was similar [62, 63]. Therefore, surgeons should not hesitate to delay closure in patients with an inadequate bladder template, as it does not risk the growth of the bladder [64]. Attempting to close a small or fibrotic bladder template places the closure at risk for dehiscence and eventual incontinence. If the bladder does not grow sufficiently within 6 to 12 months, consideration should be made for excision of the bladder or incontinent urinary diversion, such as a colon conduit.



Di Carlo HN, Maruf M, Jayman J, Benz K, Kasprenski M, Gearhart JP. The inadequate bladder template: Its effect on outcomes in classic bladder exstrophy. J Pediatr Urol. 2018 Oct;14(5):427.e1-427.e7. doi: 10.1016/j.jpurol.2018.03.023. Epub 2018 May 10. PMID: 29909193.

7 Surgical reconstruction of bladder exstrophy

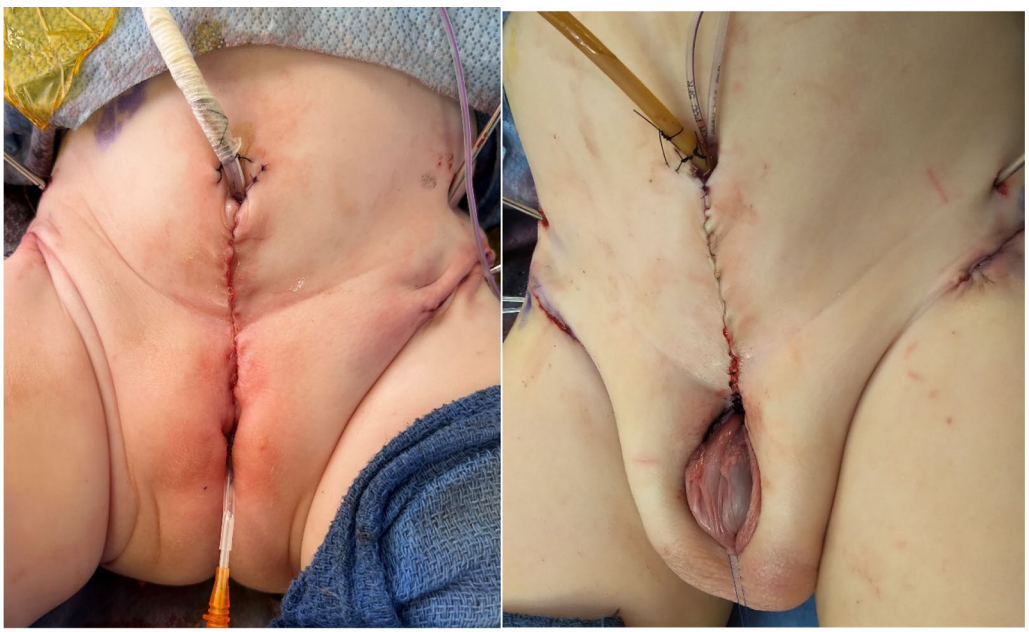
The paramount goal of surgical management of classic bladder exstrophy is a successful primary closure as it is associated with decreased overall costs, decreased inflammation and fibrosis of the bladder, improved bladder growth, and decreased need for urinary diversion [65–70]. Since the earliest description of staged surgical reconstruction of exstrophy by Sweetser et al. in the 1950's, debate has persisted regarding the ideal surgical management, timing, and technique of exstrophy closure [71, 72]. Advancements in neonatal anesthesiology and intensive care through the 1970's brought a shift toward primary closure within the first 72 h of life with a reciprocal decrease in pelvic osteotomies [72]. Pelvic osteotomy is used to deepen the pelvis, reduce pubic diastasis, and release tension on the abdominal wall but may be omitted in select neonatal closures due to pelvic malleability. Further, proponents for neonatal closure contended that early closure facilitated early bladder cycling, improved bladder capacity, and decreased risk of precancerous changes [73]. Delayed closure was primarily used for patients with inadequate bladder templates for neonatal closure (see Sect. 6.2).

Starting in the 1990's, interest in combined, all-inclusive repairs of exstrophy were rekindled for older children with failed primary closures and eventually in neonatal primary closures [60, 74–77]. Since the turn of the century, amassing data on the safety and successful outcomes of delayed closure, in combination with pelvic osteotomy, has led to ever-increasing popularity and shifts in clinical practice [72, 78–80].

7.1 Modern staged reconstruction of exstrophy (MSRE)

A detailed operative description of MSRE is provided in *Pediatric Urology* [81]. The MSRE is globally popular and represents the closure technique in up to 58% of exstrophy surgeons [82–84]. Dry urinary continence is achieved in up to 70% of MSRE patients with minimal complications [41, 79, 85].

Generally, the modern staged approach separates the repair into three stages: (1) Primary closure of bladder and abdominal wall, (2) epispadias repair, (3) continence surgeries. In recent years, timing of primary closure of the bladder and abdominal wall is customarily scheduled between 6 and 12 weeks of life [26, 72, 79, 83, 86]. Female CBE patients may also receive genitoplasty and urethroplasty with initial bladder closure. Closures may be delayed further if bladder template remains inadequate for closure (see Sect. 6.2). Prior to closure, the infant is managed with frequent saline washes of the exstrophic bladder and cellophane wrappings to protect bladder mucosa. The second stage of closure in males is urethral epispadias repair at approximately 6–10 months of age [41]. The author's institution utilizes the modified Cantwell–Ransley repair for children with an adequate urethral groove length.



Post-operative images following MSRE primary bladder closure: female (left) and male (right). As part of the MSRE approach, male patients are left epispadiac following primary closure and receive a modified Cantwell-Ransley repair at 6 -10 months of age. Courtesy of Dr. John P. Gearhart.

Once a child has received a successful epispadias repair, the patient's bladder capacity is able to be measured annually via an annual gravity cystogram under anesthesia. The third stage of closure, or continence surgery, is dependent on the child's bladder growth and desire for continence. The majority of children achieve an adequate capacity for bladder neck reconstruction (BNR) with the potential for spontaneous urethral voiding at a median age of 5.2 years [27]. In children with mild to moderate VUR, concurrent ureteral reimplantation is undertaken at time of continence surgery. Children who are not candidates for BNR, or fail to achieve urinary continence following BNR, may require bladder neck closure, augmentation cystoplasty, and/or continent catheterizable stoma.

7.2 Complete primary repair of exstrophy (CPRE)

A detailed operative description of *CPRE* is provided in *Pediatric Urology* [81]. The potential advantage of CPRE is minimalization of overall number of surgeries, hospitalizations, and associated costs of exstrophy care and improve continence rates without the need for formal bladder neck reconstruction. However, recent evidence suggests the majority of patients receiving CPRE require subsequent bladder neck reconstruction [87, 88]. CPRE combines primary abdominal wall and bladder closure with epispadias repair and partial tightening of the bladder neck [75]. Bilateral ureteral reimplantation (BUR) may also be undertaken at the time of CPRE as 50% of children will require BUR within the first year of life following CPRE alone [75, 89]. Long-term outcomes report 48% of CPRE patients achieve eventual urinary continence [88, 90].

While CPRE has many proponents among North American surgeons, there are many recognized complications [83]. The epispadias repair in CPRE is traditionally done by Mitchell Penile Disassembly whereby the urethral plate is fully dissected from the corporal bodies which renders many patients hypospadiac and necessitates later reconstruction (see Sect. 9) [91]. Other complications of CPRE include soft tissue loss [92, 93], urinary retention [94], and chronic kidney damage [95]. While CPRE is purported to reduce the number of surgeries for CBE, only 16% achieve urinary continence by CPRE alone while the vast majority require subsequent follow-up operations for reflux, incontinence, or closure failure [88, 90].

7.3 Kelly radical soft tissue mobilization repair

Developed in the late 1980's by Australian surgeon Dr. Justin H. Kelly [96], radical soft tissue mobilization technique for CBE repair was proposed as a means of closure that obviated the need for pelvic osteotomy [97, 98]. The Kelly Repair is a multistage approach including (1) bladder closure and hernia repair at birth, with (2) reconstruction of proximal urethra and associated sphincteric tissue with penile lengthening and creation of penoscrotal urethrostomy (boys only) between 3 and 6 months of age, and (3) repair of resulting penoscrotal hypospadias at approximately 3 years old [41]. The unique benefit of the Kelly technique is rooted in the radical mobilization of the pelvic floor muscles including dissection of the periosteum of pelvic girdle near attachments sites of sphincteric muscles and the pudendal neurovascular bundle [99]. Sphincteric muscles are wrapped around the reconstructed proximal urethra in an effort to provide continence. Similar to penile disassembly, the urethral plate is dissected from corporeal bodies to create the neourethra. Recent use of the Kelly Repair in single-stage delayed closures of CBE without osteotomy has shown urethral fistula and/or stenosis rates up to 30% [100].

7.4 Combined bladder closure and epispadias repair

Despite the complications and sustained need for follow-up surgery among CPRE patients, interest in combining stages of CBE repair is a popular pursuit. Combined bladder closure and epispadias repair using a modified Cantwell–Ransley technique in a highly selective patient group have been undertaken successfully as an alternative to CPRE [60, 74, 76, 93, 101]. Combined bladder and epispadias repair are particularly suited for patients with previous failed closure or primary closure beyond 5–6 months of age with an adequate bladder template (>3 cm diameter), robust urethral plate, and non-diminutive phallic length or size [60, 74, 76, 93]. Rigorous patient selection is key for minimizing complication rates and soft tissue loss. Even with this selection criteria, expected continence rates approach 60% at best [76].

7.5 Pelvic osteotomies and immobilization

Pelvic osteotomy, or surgical incision of the bony pelvis, has several benefits in application to the closure of the exstrophied bladder including a tension-free approximation of the pubis, deeper placement of the bladder and posterior vesicourethral unit within the pelvis, and improved outcomes of future reconstruction [78, 102]. Osteotomy is recommended for closures with a diastasis over 4 cm, patients over the age of 72 h, or in children with poor malleability of the pelvis as judged by a senior pediatric orthopedic surgeon [103]. Notably, the average pubic diastasis in CBE has been reported as high as 4.8 cm [41]. Several methods of osteotomy have been described within the exstrophy population including posterior iliac osteotomy, bilateral osteotomy of the superior pubic ramus, diagonal iliac wing osteotomy, and combined bilateral anterior transverse innominate and vertical posterior iliac osteotomy. The combined

transverse innominate and vertical iliac specifically have been shown to decrease rates of dehiscence and bladder prolapse compared to other forms of osteotomy [104].

Inherent to the successful impact of osteotomy on CBE closure is the critical role of post-operative pelvic and lower limb immobilization [105]. Many methods of limb immobilization have been described for post-operative management of CBE including modified Buck's traction, modified Bryant's traction, spica casting, and "mummy wrapping". Employment of immobilization methods varies widely by institution and surgical preference. Modified Buck's and Bryant's traction exert longitudinal tension along the patient's lower extremities with the legs extended while supine or with hips supinated in 90 degrees of flexion, respectively. Bryant's traction is historically used in children closed without osteotomy. Traction is maintained for 4–6 weeks postoperatively. "Mummy wrapping" and spica casting involve wrapping and casting, respectively, the extremities allowing hip flexion without abduction. Proponents of wrapping and casting note facilitation of familial bonding during immobilization and a shorter length of stay compared to traction immobilization [106]. Utilization of wraps and casts have been called into question following reports of increased rates of skin breakdown and inferior outcomes compared to Buck's or Bryant's traction [102, 107]. However, in a recent cohort of patients using spica or mummy wrapping, external fixation was found to be a pivotal protective factor in ensuring successful bladder closure [105]. In a challenge on long-held traditions, select institutions have described methods of circumventing the utilization of osteotomy or immobilization with remarkable results [108, 109].

The use of pelvic osteotomy and immobilization is not without risk. Recent reports indicate osteotomy and immobilization may increase operative times, need for blood transfusions, and risk of perioperative complications [78, 79]. Failure of inadequate osteotomy and immobilization can lead to closure failure, wound dehiscence, bladder prolapse, or loss of suprapubic tubes and ureteral stents [41]. Osteotomy complications most often include urinary tract infection, urinary fistula, transient nerve palsy, osteotomy site infection, delayed ileal union, and pin-site infection [78, 110]. Skin inflammation around pin-sites is common and often managed with oral antibiotics.

7.6 Bladder augmentation

In a recent large, survey-based, study of adult exstrophy patients, 50% of adult exstrophy patients required a bladder augmentation [111]. An augmentation cystoplasty is commonly required in CBE patients following failed primary closures and patients with noncompliant and/or insufficient bladder capacity [67, 112]. For example, approximately 40% of patients can be expected to attain adequate bladder capacity for BNR following a single failed closure, with less than half of these patients eventually becoming continent of urine [113]. Chances for continence severely dwindle with two or more failed closures. Techniques for augmentation utilize segments of bowel, stomach, or redundant ureter to expand the bladder wall.

7.7 Continent urinary diversion (CUD)

Patients requiring augmentation cystoplasty typically also require concurrent CUD. Typical CUD options include appendicovesicostomy (Mitrofanoff procedure) or tunneled ileovesicostomy (Monti procedure) to create a catheterizable stomas. Recent literature reports approximately half of adults with bladder exstrophy empty per continent stoma. Approximately 1 in 5 CUD patients report stomal leaks [111].

7.8 Ureterosigmoidostomy and Mainz Sigma pouch

Ureterosigmoidostomy (USIG), or non-refluxing reimplantation of ureters into the colon, was among the first forms of urinary diversion used in patients with CBE. In North America, use of USIG has dwindled while still being used in other parts of the world. Many patients have reverted to alternative methods of diversion due to ongoing concern for serious complications, including pyelonephritis, hyperkalemic acidosis, rectal incontinence, ureteral obstruction, and delayed development of malignancy [114, 115]. Interestingly, recent published data on long-term continence and renal preservation challenge these assertions [116–118]. Specifically, use of the Mainz Sigma pouch has distinct advantages over standard USIG with 95% of patients achieving continence [119]. Less controversy exists regarding higher rates of colorectal malignancy against this population. Colorectal malignancies are identified an average of 38 years after USIG with most common malignant pathology being poorly differentiated adenocarcinoma [118, 120]. Patients who have had mixing of urine and feces at any time during reconstruction remain at high risk for development of cancers [121, 122]. Within our institution, we only see USIG patients as adults who were treated at other locations. We recommend all patients with USIG to have yearly ultrasound and colonoscopy in adult life.

8 Management after primary closure

The initial step of the MSRE results in a patient with midpenile shaft epispadias and incontinence. Immediately following the procedure, patients spend approximately 3 days in the intensive care unit weaning from ventilation. Pain control is optimized with a combination of a tunneled epidural lidocaine administration and intravenous analgesia [123]. Before the suprapubic tube is removed, 4 weeks after surgery the bladder outlet is calibrated with a urethral

catheter to ensure drainage. Ultrasound imaging is performed to ensure status of renal pelvises and ureters. Due to the reflux that all patients will have following closure, urinary antibiotics are administered. Imaging is repeated 3 months after discharge and thereafter at intervals of 6 months to 1 year at the surgeon's discretion, typically for 2–3 years. Prophylactic antibiotics will be given continuously until ureteral reimplantation is carried out, typically performed alongside epispadias repair in the modern staged approach at time of continence procedure. Yearly cystoscopy with cystography under anesthesia is carried out to estimate bladder growth and to evaluate reflux [47]. Dilation of the urethra or intermittent catheterization may prove necessary in patients who develop increased outlet resistance and recurrent infections [124].

9 Penile and urethral closure in exstrophy

Epispadias repair and penile reconstruction, typically performed between 6 and 10 months of age with MSRE, corrects dorsal chordee, urethral and glandular reconstruction, and penile skin closure [76]. Intramuscular or topical testosterone can improve the quality and quantity of penile skin as well as size of the urethral plate and should be a preoperative consideration with penile closure [125]. The modified Cantwell–Ransley epispadias repair is performed by advancing the urethral meatus to an orthotopic position by utilizing a reverse meatal advancement and glanuloplasty technique [126]. Dorsal chordee is simultaneously released by mobilizing the urethral plate from the corpora from the level of the glans to the prostatic urethra. The corporal bodies are then anastomosed over the dorsal medial aspect of the tubularized urethra. In 1996, Mitchell and Bagli described an additional modification to the Cantwell–Ransley repair, where the urethral plate, corporal body, and hemiglans are dissected free from each other [91]. This repair, dubbed the "Complete Penile Disassembly", was justified owing to the separate blood supply of each corpora. This repair has been criticized for inducing ischemia in the urethral plate as it shares blood supply with the spongiosum. Lateral dissection, during Mitchell repair, can lead to neurovascular bundle injury and subsequent erectile dysfunction [127]. Mitchell repair, often done in conjunction with CPRE, can often lead to a tubularized urethra being shorter than the corpora, resulting in hypospadias and necessitating a subsequent complicated hypospadias repair [128].

10 Exstrophy reconstruction failures and complications

10.1 Failed closure

Failure can occur during any step of reconstruction manifesting as bladder dehiscence, bladder prolapse, vesicocutaneous fistula, or neourethral stricture and urinary obstruction [129]. A failed primary closure decreases eventual bladder capacity, chance of spontaneous voided continence, and leaves a lasting negative financial impact [113, 130, 131]. These studies highlight the importance of initial successful closure; therefore, surgeons with minimal experience should consider referral to large centers with experience in treating exstrophy.

Dehiscence or prolapse, possibly due to inadequate pelvic immobilization, abdominal wound tension, or incomplete mobilization of the pelvic diaphragm, requires a 4–6 month recovery period before a secondary closure should be attempted [74, 132]. In certain select patients with failed closure, a combined bladder closure and epispadias repair may be attempted (see Sect. 7.3). After failure of primary CBE closure, the chance of achieving the bladder capacity necessary for BNR, >100 cc, reduces to 60% [112]. Bladders that do not reach this goal capacity can be augmented, typically with colon or small bowel to expand the bladder wall.

10.2 Failed bladder neck repair

Some patients may remain incontinent after bladder neck reconstruction secondary to a small bladder capacity, decreased compliance, or inadequate outlet resistance. Failure of bladder neck repair is defined as inability to achieve continence, or a 3-h dry period within 2 years after BNR. In those approaching daytime continence, >2 h dryness, urethral bulking agents may be used to avoid further reconstruction, but the majority of failed BNR patients require augmentation or continent urinary diversion [133].

10.3 Failed genitourethral reconstruction

Historically there have been few complications following epispadias repair, however, with the advent of the complete penile disassembly more significant complications including loss of the glans, corpora, penile skin, and urethral plate have been reported [76]. Reconstructing these complications may require the use of tissue expansion, buccal mucosa grafting, or full thickness skin grafting. Radial forearm neophalloplasty remains an option for patients with significant penile loss, allowing patients a cosmetic, sensate phallus. For older patients, phallus cosmesis may require further management, with penile scars and short phallus as the most common complaints. Scar revision could require flaps or skin grafting to ensure enough penile skin is available to close in a plastic fashion. Freeing scar tissue and suspensory ligaments may provide additional length to the phallus, but aggressive attempts to lengthen the penis should be cautioned due to the great risk of corporeal denervation and devascularization.

11 Transitional exstrophy patient: adolescent and adult concerns

With innovation and improved CBE surgical management over the last several decades, the childhood survival rate of CBE has increased drastically. As a result of improved management, care for adolescent, adult, and geriatric patients born with bladder exstrophy are an active area of research.

Children with CBE transitioning into adulthood require increasing need to address both long-term functional and psychological aspects of dealing with a multiorgan birth defect. Management of this major congenital defect through multiple reconstructive surgeries predisposes patients to problems of urinary incontinence and sexual dysfunction. As such, it is important to address these topics with the patient and their caregivers from an early age. While research suggests that children with exstrophy do not have clinical psychopathology, many individuals struggle psychologically with adapting their medical care to their desired lifestyle, self-esteem, and social functioning [134]. Notably, urinary incontinence can be particularly stressful for individuals; therefore, reconstructive efforts to obtain dryness once the child is ready carries potential psychological benefit.

11.1 Quality of life

As survival becomes increasingly universal, health-related quality of life (QoL) is becoming an increasingly important topic and driver of reconstructive techniques. Early reports on QoL reported mixed results from decreased QoL in all post-reconstructive patients, to comparable QoL with peers, to increases in QoL among adolescents [135–137]. Parents specifically report significantly impaired adolescent general health, family activity, and increased parental emotional distress [137, 138]. As expected, patients with urinary incontinence tend to report lower QoL metrics [139].

11.2 Male sexual function and fertility

In the BEEC, the penis is 50% shorter and 30% wider compared to normal adult males due to the increased intercorporal and intrasymphyseal distances from the pubic diastasis [35]. Additionally, there is a congenital shortage of anterior corporal tissue and a deep linear scar on the dorsum-lower abdominal wall from which it tethers penis. As BEEC, patients sexually mature penile appearance and function are the focus of reconstruction during late adolescence and early adulthood. The penis is lengthened by incising remnants of the suspensory ligaments before using tissue expanded (TE) penile shaft skin or a full thickness skin graft (FTSG) to provide soft tissue coverage [140–142]. Alternatively, a neo-phallus is used for patients where the penis would be too short for penetrative intercourse despite lengthening or those with aphallia, particularly in cloacal exstrophy.

The radial forearm free flap (RFFF) and the pedicled anterolateral thigh flap (PALTF) are the most frequently used techniques for phalloplasty in BEEC [143, 144]. The decision to perform RFFF or PALTF is dependent on vascular anatomy of the non-dominant arm and vascular integrity of the lower abdomen for microsurgical anastomosis of blood vessels. Surgeons should account for patient preference including tactile and erogenous sensation or donor site morbidity and flap bulk. 1 year after phalloplasty, patients undergo insertion of an inflatable penile prosthesis. However, patients do not undergo urethral reconstruction, secondary to the increased risk of complications in BEEC, and patients may have undergone continent urinary diversion [145, 146].

Penile lengthening with TE or FTSG and phalloplasty all resulted in better perception of penile length [147]. Phalloplasty produced the greatest improvement in perception of length though penile lengthening patients reported better sensation. Surgical decision requires careful planning on the most suitable technique while taking patient preference into consideration, and all patients should receive pre- and post-operative psychological evaluation [148].

Adult BEEC males have similar concern with sexual health and relationships as unaffected males. Most have attempted engaging in sexual intercourse with missionary (36.5%) and cowgirl (23.8%) being the most effective positions, attributable to the congenital shortage of anterior corporal tissue [149]. If patients want to father children, assisted reproduction is often necessary (48.0–53.3% of patients) because of infertility from retrograde ejaculation, low or no sperm concentration, or poor sperm motility [149, 150].

11.3 Female sexual function and fertility

Concerns regarding sexual function among females with CBE are predominantly three-fold: appearance of external genitalia, adequacy of vaginal opening, and uterine prolapse. Although initial correction of female external genitalia is undertaken at time of primary closure, surgical revision is frequently performed at puberty. Recurrence of pubic diastasis following closure may lead to flattening of mons pubis, separation of pubic hair, and/or separation of clitoral halves. The vaginal orifice is more vertical and stenotic in appearance, which can be resolved with local tissue rearrangement and post-operative dilation [151, 152]. Uterine prolapse occurs more frequently, and at younger ages, in women with CBE [153]. As many as 60% of pregnant CBE women will develop prolapse [147, 154, 155]. In this population, uterine suspension was only modestly successful leading many

experts to recommend uterine fixation [152, 156, 157]. Prophylactic uterine suspension should be considered to prevent prolapse [154, 158].

Sexual desire is reportedly normal in adult women, and most are sexually active [149, 153]. Average age for commencement of sexual activity was 20 years and outside of a few complaints of dyspareunia, most indicated normal orgasms [153]. In some cases, sexual activity was restricted due to perceived cosmetic appearance of external genitalia.

Fertility among women born with CBE is generally preserved with up to 66% of women attempting conception able to achieve successful pregnancies [149, 159]. Cervical and uterine prolapse and temporary urinary incontinence are common complications following pregnancy [149, 160]. Pregnancy in a woman with bladder exstrophy remains high risk for both the mother and the fetus and warrants referral to a tertiary care center for obstetrical care [159]. In most cases, planned cesarean section with a trained urologist present and/or involved in the delivery appears to be the safest mode for delivery.

12 Conclusion

Classic bladder exstrophy is a debilitating multi-system malformation that proves a formidable challenge to even the most experienced of surgeons. Modern advances in the management of CBE including prenatal diagnosis, delayed operative timing, use of pelvic osteotomy with pelvic and extremity immobilization help to optimal closure outcomes. Long-term urinary continence, cosmesis, sexual function, and fertility among these patients continue to present new challenges for the upcoming generation of pediatric and reconstructive urologists.

Abbreviations

BEEC	Bladder exstrophy-epispadias complex
OEIS	Omphalocele, exstrophy, imperforate anus, and spinal abnormalities
CBE	Classic bladder exstrophy
CE	Cloacal exstrophy
MRI	Magnetic resonance imaging
MSRE	Modern staged reconstruction of exstrophy
CPRE	Complete primary repair of exstrophy
BNR	Bladder neck reconstruction
VUR	Vesicoureteral reflux
BUR	Bilateral ureteral reimplantation
CUD	Continent urinary diversion
USIG	Ureterosigmoidostomy
QoL	Quality of life
TE	Tissue expanders
FTSG	Full thickness skin graft
RFFF	Radial forearm free flap
PALTF	Pedicled anterolateral thigh flap

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Author contributions

All authors have read and approved the manuscript for submission. CCM was contributed to idea creation, literature review, manuscript preparation, critical review. AH was contributed to literature review, manuscript preparation, critical review. TGWH was contributed to literature review, manuscript preparation, critical review. CC was contributed to literature review, critical review. JPG was contributed to idea creation, manuscript preparation, critical review. All authors read and approved the final manuscript.

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Declarations

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This research adheres to the ethical research criteria established and approved by our institutional review board.

Consent for publication

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