Evaluating Outcomes of Enterocystoplasty in Patients With Spina Bifida: A Review of the Literature

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Purpose: The urological complications of spina bifida impose a significant burden of disability and disease. Therapy is focused on the bladder to achieve the primary goals of maintaining normal renal function and attaining urinary continence. When medical management fails, surgical intervention, including enterocystoplasty, is frequently performed. However, practice patterns for enterocystoplasty show significant variation. Given this context, we examined outcome measures for enterocystoplasty in patients with spina bifida.

Materials and Methods: A MEDLINE® search was performed for articles on enterocystoplasty in patients with spina bifida. A total of 226 articles were identified and manually reviewed for relevant studies. Additional articles were selected based on a cited reference search.

Results: Almost all studies are retrospective, single institution case series of a relatively small number of patients. Few uniform or validated outcome measures for enterocystoplasty exist but reported measures typically include urodynamic, continence and satisfaction parameters. Interinstitutional variability in urodynamic measurements and in definitions of continence makes a comparison of outcomes difficult. The complication rate following enterocystoplasty is significant, well described and primarily related to the use of gastrointestinal segments for urine storage.

Conclusions: Medical management is the mainstay of neurogenic bladder therapy in the spina bifida population. Enterocystoplasty remains an important option to prevent or reverse upper tract deterioration, and/or improve or cure socially unacceptable incontinence despite poorly defined outcome measures. The development of appropriate and validated outcomes measures may enable more uniform, effective and safe urological care of patients with spina bifida.

Key Words: urinary bladder, neurogenic; spinal dysraphism; physician's practice patterns; gastrointestinal tract; transplants

More than 90% of patients with spina bifida have neurogenic bladder dysfunction, which can manifest as renal deterioration, recurrent urinary tract infection and/or urinary incontinence.[1] Before modern therapy the urological complications of spina bifida were a significant cause of mortality in those who survived the first few years of life with its attendant neurosurgical mortality. Medical management has significantly decreased the morbidity of this disorder with the advent of CIC and anticholinergic medications. In those in whom medical therapy fails enterocystoplasty has been performed to lower bladder storage pressures and increase bladder capacity. Unfortunately the short-term and long-term complication rates of enterocystoplasty remain high and potentially serious. This has led groups at some centers to begin earlier and more aggressive medical therapy in an attempt to decrease the need for enterocystoplasty.[2] However, significant variation exists in enterocystoplasty practice patterns and rates of enterocystoplasty do not appear to have decreased recently, in contrast to results in single institution series demonstrating the decreased use of enterocystoplasty with aggressive medical management.[3] Thus, we reviewed the reported outcomes of enterocystoplasty in patients with spina bifida with particular attention to indications, outcome measurement and safety issues.

METHODS

A MEDLINE search was performed for articles on enterocystoplasty in patients with spina bifida. Articles were limited to human patients and the English language. The initial search was limited to articles from 1982 to 2007 because this time represents most of the modern published experience with enterocystoplasty. A total of 226 articles were identified and manually reviewed for studies relevant to the objectives of the current review. Additional articles were selected from a cited reference search with some articles predating 1982 to accomplish specific review objectives.

RESULTS

Methodology Assessment

Overall scientific knowledge regarding enterocystoplasty is based on relatively small studies, primarily single institution case series. The statistical methods of these studies are often limited or absent. This is reflective of the low level of evidence in the pediatric urology literature, in which randomized, controlled trials represent less than 1% of pub-

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lished studies compared to approximately 10% in the adult urology literature.[4,5] Bias toward the publication of positive studies is a well documented phenomenon that further compromises objective assessment. The current report summarizes the best available, although suboptimal, evidence on which current practice is based.

Evolution of Care for Neurogenic Bladder in Patients With Spina Bifida

Treatment in children with spina bifida has evolved dramatically in the last 40 years. Before improvements in neurosurgical care children with spinal dysraphism rarely lived into late childhood or adolescence and, thus, the urological complications of this disease were seldom known, identified or treated. However, by the 1970s these children were living longer and the urological consequences of the disease mandated further study and intervention. Initially intervention primarily meant urinary diversion, typically an ileal conduit, to manage infection, incontinence or upper tract deterioration.

Management for neurogenic bladder was revolutionized in 1972 by the introduction of CIC by Lapides et al.[6] CIC provides regular and complete bladder emptying and, therefore, it can prevent increased filling pressure in poorly compliant bladders or overflow incontinence in poorly contractile bladders. Anticholinergic medication used in concert with CIC can further decrease bladder pressure and improve incontinence by its inhibitory effects on the detrusor. Avoiding increased bladder pressure is critical for preventing or reversing upper tract deterioration, as documented in multiple long-term studies.[2] However, in small or poorly compliant bladders medical therapy combined with CIC may not be adequate to achieve safe storage pressure. Surgery may be necessary to divert urine away from the hostile bladder, as was popular before the 1970s, or alter bladder storage characteristics. CIC made possible the popularization of augmentation cystoplasty by providing a mechanism to empty the altered bladders, which rarely empty spontaneously.

To date only patient urothelial or enteric tissue has routinely been used to augment the bladder. Urothelial tissue is an ideal substitute for augmentation because it is neither absorptive nor secretory but unfortunately rare is the patient who has excess ureteral tissue to add to the bladder. Therefore, enterocystoplasty with gastrointestinal segments has been the mainstay of augmentation cystoplasty. In the last quarter century, as patients with spina bifida have survived longer and been mainstreamed more, enterocystoplasty has become an increasingly common surgical tool in the urological treatment of these patients. The number of bladder augmentations in children in the United States was fairly constant from 1997 to 2003 at an estimated 700 annually according to the Agency for Healthcare Research and Quality.[7]

To decrease the possible future need for enterocystoplasty some investigators have advocated the aggressive commencement of medical therapy beginning at birth to enhance bladder growth. However, there is little understanding of enterocystoplasty practice patterns outside of published single institution series. Lendvay et al reported wide institutional variability in the proportion of children with spina bifida undergoing enterocystoplasty in the United States.[3] At specialty centers the average proportion of patients with spina bifida who have undergone enterocystoplasty is 5.4% as a percent of unique spina bifida inpatient visits but it ranges widely from 0.5% to 16%. Enterocystoplasty at high volume centers (10 or greater per year) were performed in younger patients than those at low volume centers but the clinical significance of a 2-year difference in ages is debatable.[3]

Indications for Enterocystoplasty

The wide variation in bladder augmentation practice mandates an understanding of the indications for the procedure. Broadly speaking the indications for enterocystoplasty can be absolute in the setting of upper tract deterioration due to high bladder storage pressure that is refractory to medical therapy. More commonly the indications are relative in the setting of socially unacceptable incontinence due to small capacity, detrusor overactivity and/or decreased compliance. The relative nature of the latter indication may partially explain the considerable institutional variation in enterocystoplasty rates, although this variation is likely multifactorial. Provider related factors may include comfort with the complex and time-consuming procedure as well as personal beliefs regarding the benefits vs the potentially high complication rate of the procedure. Patient related and parental factors likely relate to the varying desire for urinary continence, the willingness to perform CIC and the fear of major surgery. Institutional factors, such as a specialized spina bifida clinic and the necessary infrastructure to care for patients after enterocystoplasty, may also influence practice variation.

The most objective indication for bladder augmentation is a documented bladder pressure of greater than 40 cm H_2O. Increased bladder pressure can be seen intermittently due to detrusor overactivity or pressure may increase steadily during filling due to decreased compliance. Detrusor leak point pressure is determined when resting bladder pressure exceeds the pressure exerted by the bladder outlet and leakage occurs. This value of 40 cm H_2O emanates from a 1981 study by McGuire et al, who observed that detrusor leak point pressure above that level was strongly associated with upper urinary tract deterioration in a case series of 42 patients with spina bifida followed a mean of 7.1 years.[8] Subsequently these investigators noted that medical treatment with CIC and anticholinergics for increased detrusor leak point pressure decreased the probability of future upper tract deterioration, eg hydronephrosis, vesicoureteral reflux and decreased renal function.[9] Other investigations suggest that pathogenic changes in bladder tissue may occur even at a storage pressure of less than 40 cm H_2O.[10] Despite limited controlled clinical data it has become generally accepted that storage pressure that is chronically above 40 cm H_2O is pathogenic and should be treated.

When medical therapy fails to decrease increased bladder pressure, enterocystoplasty is frequently performed to increase bladder capacity and/or decrease bladder storage pressure. Some patients have a weak outlet and leakage may occur before bladder storage pressure attains a deleterious level, which is theoretically more than 40 cm H_2O. However, urinary continence may be impossible to achieve by bladder augmentation alone. Therefore, some patients may also require procedures to increase bladder outlet re-

sistance to increase Valsalva leak point pressure. If so, patients almost universally require CIC postoperatively to assist with bladder emptying. When CIC cannot be performed via the urethra, a continent catheterizable channel may be necessary to allow CIC via an abdominal stoma.

While the term enterocystoplasty refers simply to the surgical addition of a bowel segment to the bladder, significant variation in the technique and in the bowel segment used complicates outcomes analysis. Augmentation with gastric, small bowel and colonic segments are well established in the literature, while variations in the length and configuration of bowel segments further contribute to the heterogeneity of study cohorts, creating additional challenges when comparing outcomes.

Outcome Measures Following Enterocystoplasty

Uniform, objective and validated measures for outcomes are lacking in the enterocystoplasty literature. Urodynamic data, ie bladder pressure and capacity, are frequently published postoperative outcomes but there is disagreement on the actual need for urodynamic studies after enterocystoplasty.[11] Significant interinstitutional differences exist in urodynamic techniques, such as the rate of bladder filling, catheter size, fluid temperature and patient positioning.[12] Most series document an improved post-enterocystoplasty bladder pressure at capacity of 7 to 20 cm H_2O, although higher pressure has been documented.[11,13,14] Ideally pressure should be measured at functional bladder capacity, eg the specific bladder capacity of the patient, as identified by the maximal catheterized volume. The use of bladder capacity as an outcome after enterocystoplasty is confounded by the dynamic bladder capacity in a growing child and the lack of a consensus on age or weight based calculations of bladder capacity in children with spina bifida, who are often small for their age. Uncertainty exists regarding the optimal outcome measure for bladder volume. Should outcomes report the final volume, a percent increase in volume or a fixed volume increase? The reported augmented bladder capacity is typically 330 to 600 ml.[11,13,14] These results appear durable with various series documenting stable increases in bladder capacity and decreases in bladder pressure out to a mean followup of 8 years.[11,13,14] Longer term studies do not exist or they could be biased by loss to followup as children age and potentially transfer care to other providers.

While urodynamic studies are clearly not performed in every patient with augmentation, imaging is another outcome measure following enterocystoplasty. Variation exists in the choice of postoperative imaging studies and intervals among centers due to a lack of consensus.[14] If upper tract dilatation is present before surgery, it is necessary to document postoperative improvement. Renal ultrasound is the mainstay of imaging for outcomes assessment along with voiding cystourethrogram when reflux was present preoperatively.

Patient centered outcomes are particularly important following enterocystoplasty, especially when the procedure is performed to address the quality of life concern of socially unacceptable incontinence. Reported postoperative continence rates are typically 82% to 100% with CIC, although these results are potentially biased by the lack of data on preoperative continence rates.[15,16] Continence measures vary but they include pad counts and self-reported incontinence, which may be based on a physician chart report or patient completed forms. Pad weight, which is commonly reported in treatment for incontinence in women, is infrequently used in patients with spina bifida, particularly if the patient also has fecal incontinence. Reported continence measures after enterocystoplasty can be problematic due to variable definitions of the dry interval (eg 2, 3 or 4 hours), compliance with the CIC regimen and bladder neck competence.

Aside from published continence rates, few quality of life studies exist in this patient population. The Qualiveen questionnaire and the International Consultation on Incontinence Questionnaire–Short Form have been used to assess patients following enterocystoplasty[17,18] but comparisons of preoperative and postoperative quality of life are lacking. Furthermore, neither instrument has been validated in the spina bifida population.[17,18] Patient satisfaction assessments following enterocystoplasty for neurogenic bladder, not limited to spina bifida, have been published. Overall patients report acceptable satisfaction with enterocystoplasty despite less than perfect continence and a not insignificant complication rate.[13] However, satisfaction scores must be interpreted in the context of the degree of impairment in preoperative quality of life (ie the severity of urinary incontinence and whether the patient also requires diapers for fecal incontinence), the limited alternatives to enterocystoplasty, the potential response bias (eg satisfied patients are more likely to respond), a potential administration bias (eg reported satisfaction may be higher when data are collected by the surgeon or extender instead of a neutral party), variable perceptions of normalcy due to abnormal mental development or socialization in some patients with spina bifida and the lack of validated satisfaction measures in this population.

Complications of Enterocystoplasty

Complications are especially important outcomes to examine following enterocystoplasty. Approximately a third of patients experience postoperative complications.[19] These complications are the result of a number of factors, including surgical technique, inherent properties of the bowel segment and patient compliance with maintenance regimens.

Re-augmentation. Overall the proportion of patients requiring re-augmentation following cystoplasty is 3.7% to 5.9% based on a maximum followup of 10 years.[20] In these series re-augmentation was required in a higher proportion of cases using gastric or colonic segments than in cases using ileum, although these differences were not statistically significant in all studies for gastric, colonic and ileal segments (10.3%, 4% to 13.8% and 0% to 1.4%, respectively).[20] Primary causes of failure are the incorporation of an inadequate amount of gastrointestinal segment, shrinkage of the gastrointestinal segment and periodic uninhibited contractions causing increased bladder pressure above 40 cm H_2O, most notably in colonic segments. The need for re-augmentation can be minimized with appropriate attention to technical detail, such as detubularizing bowel segments to create a spherical bladder to the greatest extent possible. Augmentation shrinkage may be due to ischemia of the bowel seg-

ment and it may be greater with gastrocystoplasty, given the longer mesentery required.

Gastrointestinal effects. Following enterocystoplasty the rate of bowel obstruction is 3% to 10%.[21,22] It can be minimized by technical considerations, eg appropriate mesentery closure to prevent internal herniation. Diarrhea following enterocystoplasty is rare but the rate of chronic diarrhea has been documented to be as high as 10% to 23% when the ileocecal valve is removed.[23] Gastrointestinal symptoms may be due to the interruption of bile acid circulation, while loss of the terminal ileum may alter bile salt absorption, leading to steatorrhea and ultimately to diarrhea. Bowel dysfunction in the form of flatus leakage, fecal urgency and fecal incontinence has been documented in 30% to 40% of patients and persistent gastrointestinal symptoms have been noted in 40% to 50% of adults with 8 years of followup after various enteric procedures for urinary reconstruction/diversion.[24] The applicability of this finding to pediatric patients with spina bifida is unclear.

From the nutritional perspective vitamin B12 malabsorption can occur if a critical length of terminal ileum is removed from the fecal stream, which may result in megaloblastic anemia and/or irreversible peripheral neuropathy. Low serum B12 has been reported in 10% to 14% of children who undergo ileal urinary diversion.[25,26] Therefore, the distal 20 cm of ileum should be avoided for cystoplasty and patients should have serum B12 levels chronically assessed after ileum is used for reconstruction.[27] Other nutritional deficiencies have not been noted due to the great redundancy of the digestive system for absorbing other essential nutrients.

Metabolic complications. The intact bladder stores urine with minimal absorption of urinary components but incorporation of an enteric segment places an absorptive and secretory membrane in contact with urine. Potential metabolic derangements depend on the type of bowel segment used for urinary augmentation (see table). Hyperchloremic metabolic acidosis is the most common metabolic complication of enterocystoplasty. It is thought to arise primarily from the resorption of ammonium and chloride from urine back into the bloodstream. Almost all patients undergoing bladder augmentation with intestinal segments also have a decrease in serum bicarbonate, although clinical metabolic acidosis is rare when renal function is normal.[21] Conversely gastrocystoplasty can result in hypokalemic hypochloremic metabolic alkalosis due to the stomach secretion of hydrogen, potassium and chloride ions into urine.[28] Groups at some centers prefer to use gastric augmentation in the setting of renal impairment because metabolic acidosis is prevented. However, this must be weighed against the fact that hematuria-dysuria syndrome may develop in patients with gastrocystoplasty as a result of low urine pH.[29] The excessive acidity of urine following gastrocystoplasty can also create skin irritation if patients remain incontinent following surgery.

Potential serum electrolyte derangements associated with specific gastrointestinal segment use for bladder augmentation

Segment	pH Balance	Serum Na^+	Serum K^+	Serum Cl^-
Stomach	Alkalosis	—	Decreased	Decreased
Jejunum	Acidosis	Decreased	Increased	Decreased
Ileum	Acidosis	—	Decreased	Increased
Colon	Acidosis	—	Decreased	Increased

Delayed growth has been noted in a single study of patients with spina bifida undergoing enterocystoplasty but the study design was limited by the lack of a comparison group without augmentation cystoplasty.[30] Similar observations have been subsequently noted in patients with bladder exstrophy who underwent enterocystoplasty.[31] While these bladder exstrophy series had comparison groups, each had a small sample size. In contrast, a more recent investigation primarily in patients with bladder exstrophy-epispadias revealed a normal distribution of height after enterocystoplasty, although patients with myelomeningocele or sacral agenesis were excluded from study.[32] A mechanism of decreased height may be the effect of subclinical acidosis on bone mineral density and growth.[33] Acidosis is not usually seen clinically because buffers are leached from bone to counteract the potential acidosis caused by enterocystoplasty and maintain normal serum pH and bicarbonate. However, this balance occurs at the cost of progressive bone demineralization. Further investigation is needed to understand the growth outcomes and biological mechanisms of this phenomenon as well as the longer term implications for bone health, such as premature osteoporosis in early adulthood.

Bacteriuria and infection. Bacteriuria is common, if not universal, following enterocystoplasty. CIC is known to introduce bacteria, while the altered bladder surface, presence of mucus and incomplete bladder emptying by catheter may promote bacterial growth.[34,35] In this setting differentiating bacterial colonization and infection can be difficult for clinicians and outcome investigators alike. Bacteriuria treatment is typically indicated only for symptoms of infection, including new onset incontinence, suprapubic pain, hematuria, foul smelling urine or fever, or for urea-splitting organisms that may contribute to bladder stone formation.[36]

Mucus. Gastrointestinal segments secrete mucus into urine after enterocystoplasty, which can persist throughout life. Colonic segments produce the greatest amount of mucus, followed by ileal and then gastric segments. Mucous plugging of catheters can impede drainage of the augmented bladder. Mucus is thought to provide a nidus for urinary tract infection and/or calculus formation. Some experts suggest that routine irrigation may minimize these complications, although efficacy depends on patient compliance, the irrigation solution and the catheterization route.[37] Irrigation via urethral catheterization is likely more effective for evacuating mucus than via an abdominal stoma because the urethral catheter can better access the accumulated mucus in the dependent portion of the bladder. Instilling mucolytics can be helpful in problematic cases.

Calculi. Bladder calculus formation is a frequent long-term complication of enterocystoplasty with an incidence of 6% to 52%.[22,38] The most significant factors contributing to stone formation are poor emptying and mucous accumulation in the augmented bladder.[39] However, technical factors, such as the use of nonabsorbable sutures during augmentation, can also provide a nidus for stone formation. Bacteri-

uria and altered urinary pH may also contribute to stone formation and growth following enterocystoplasty. Symptoms of bladder calculi can include pyuria and frequent urinary tract infections, rather than pain, because the bladder and urethra are frequently insensate in these patients. Irrigation may decrease bladder mucus and, therefore, decrease calculus formation.[37] Renal stones, which may also be identified more frequently after cystoplasty, were noted in 1 study in 16% of patients with spina bifida who had an augmented bladder.[40] In addition to infection with urea-splitting organisms, hypocitruria may explain the increased incidence of upper urinary tract stones.[40]

Pregnancy. Managing pregnancy following enterocystoplasty should focus on delivering a healthy baby, while preserving renal function and continence in the mother.[41] Urinary tract infections should be treated aggressively.[42] Serum creatinine should be monitored monthly and the upper tracts should be imaged with ultrasonography if serum creatinine increases.[43] The detection of preeclampsia traditionally relies on the presence of proteinuria. However, serum uric acid analysis is preferred to detect preeclampsia in patients with enterocystoplasty since intestinal mucous production may show false-positive results on dipstick urinalysis for protein. Cesarean section is typically recommended over vaginal delivery to prevent damage to the poorly innervated pelvic floor in patients with spina bifida. A reconstructive urologist familiar with enterocystoplasty may need to be present at cesarean section to assist with preserving the augmented bladder because the mesentery can lie between the abdominal wall and the uterus.

Delayed spontaneous bladder perforation. Spontaneous bladder rupture is a potentially fatal complication of enterocystoplasty that has been documented in 4% to 10% of patients.[19] Perforation typically occurs in the bowel segment (67% to 82% of cases), rather than at the bowel-bladder anastomosis.[44] The pathogenesis of spontaneous bladder perforation is believed to be chronic over distention caused by poor compliance with catheterization.[45] Local ischemia due to impaired perfusion of the distended bowel segment weakens the augmented bladder wall, leading to perforation. Bladder perforation can spill bacteria into the peritoneum, which is a particularly grievous injury in a patient with a ventriculoperitoneal shunt. Clinicians must be aware of the potential for a fatal outcome. The acute abdomen in these patients warrants aggressive evaluation that must include cystography. Computerized tomography and abdominal ultrasound may also be useful adjuncts to cystogram because these studies can reveal intraperitoneal fluid even in the presence of a negative cystogram.[46] The acute abdomen in patients with spina bifida frequently requires surgical exploration, drainage and repair, and mortality is significant (14%) even with aggressive management.[47]

Malignancy. Bladder malignancy in patients with enterocystoplasty is a particularly concerning complication because the malignancy is likely secondary to surgery that was likely performed for quality of life indications, rather than for a life threatening disease. To our knowledge the true incidence of post-enterocystoplasty malignancy is unknown. At least 51 cases of malignancy following augmentation cystoplasty have been reported in the literature, including adenocarcinoma and transitional cell carcinoma.[48,49] In the largest reported series of bladder augmentation the incidence of malignancy was 0.6%.[50] In approximately 90% of these cases enterocystoplasty was performed in adults for indications other than neurogenic bladder, ie a contracted bladder secondary to tuberculous cystitis.[48] Recent reports have documented malignancy in patients with spina bifida following enterocystoplasty with small bowel and gastric tissue.[48] However, it is difficult to determine what risk is independently attributable to augmentation vs other risk factors. Carcinogenesis in this setting is likely multifactorial. Leading theories include potentially carcinogenic substances, ie epidermal growth factor, in urine, chronic inflammation and increased cyclooxygenase-2 expression with local prostaglandin formation.[49] Despite this uncertainty malignancy is a particular concern when the life expectancy of children undergoing bladder augmentation is many decades longer than that in adults undergoing bladder reconstruction after radical cystectomy. Soergel et al estimated that the risk of bladder malignancy in children undergoing enterocystoplasty for neurogenic bladder may be as high as 1.2% at 10 years.[48] For this reason it is mandatory that patients with enterocystoplasty undergo lifelong surveillance with annual cytological evaluation and at least biannual cystoscopy beginning no later than 10 years after enterocystoplasty.

CONCLUSIONS

Significant variation exists in the rate of enterocystoplasty in the United States, likely because of relative indications, and variable provider and patient beliefs about the procedure. Despite this variation enterocystoplasty remains an effective tool for decreasing bladder pressure, preventing or reversing upper tract deterioration and managing socially unacceptable incontinence in patients with spina bifida in whom medical therapy fails. However, uniform, objective and validated outcome measures for these goals are lacking. The current understanding of outcomes is based primarily on retrospective, single institution series that may reflect publication bias. Complications following cystoplasty are frequent and related to the use of intestinal segments. Overall reported outcomes are remarkable for a high continence rate and acceptable patient satisfaction but at the cost of complications in approximately a third of patients. Identifying methods to avoid or prevent the complications of augmentation cystoplasty remains one of the primary challenges of surgical management for neurogenic bladder.

Abbreviations and Acronyms

CIC = clean intermittent catheterization

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