Metabolic and Long-Term Consequences of Enterocystoplasty in Children: A Review

FROM THE GUEST EDITORS

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Enterocystoplasty is a common procedure in pediatric urology today. It is used in children born with developmental abnormalities involving the genitourinary system, and has become a standard part of our armamentarium for the management of neurogenic bladder as well as myogenic bladder. Although the principles involved in enterocystoplasty are fairly standard, various techniques and various bowel segments can be used depending on the clinical situation. The incorporation of any bowel segment into the genitourinary system can be associated with several and varied metabolic and mechanical consequences. The old adage that urothelium is the best substitute for urothelium remains true, the problem is that we often do not have a ready source of urothelium. The gastrointestinal tract is a relatively poor substitute for urothelium. It is semipermeable and permits non-physiologic fluid and electrolyte absorption which often leads to metabolic abnormalities. Further complicating matters, the loss of various portions of the gastrointestinal tract can interfere with normal gastrointestinal function, resulting in complications such as chronic diarrhea, which alone carries additional metabolic consequences. Many of these problems have been documented in the literature over a number of years and we will attempt in this issue of the Dialogues to point out several specific problems associated with various bowel segments incorporated into the genitourinary system as well as some of the long-term concerns with the use of bowel as a bladder substitute in children.

FROM THE EDITOR

Anthony A. Caldamone, M.D.

Identification and proactive aggressive management of the neuropathic bladder and other congenital bladder anomalies has resulted in a modest decrease in the number of hostile bladders that are refractory to intermittent catheterization and anticholinergic therapy. However, in spite of these efforts, surgical management of the hostile bladder remains a significant part of pediatric urology. While this has become a routine part of our armamentarium, we must continue to recognize the short-term and long-term consequences of reconstruction using bowel segments. The development of reliable alternatives to bowel which would potentially avoid many of the consequences discussed in this issue has been slow in coming.

This issue of Dialogues represents a career’s worth of experience in managing children who have had urinary tract reconstruction using bowel segments. Drs. Hensle and Gilbert provide a superb review of both short-term and long-term complications in this select population. I applaud the authors for this comprehensive overview which I am certain will become a significant resource for all of us in the field.
DPU: Just by way of background, how did you develop an interest in metabolic problems associated with enterocystoplasty?

TWH: I think this comes from my early work during surgical training with total parenteral nutrition (TPN). We were on the forefront of developing TPN as a standard form of medical treatment and as part of that I developed an interest and some expertise in both nutrition and metabolic issues in children and adults.

DPU: In talking about enterocystoplasty, where should we start?

TWH: We probably ought to start at the bottom and work up. Ureterosigmoidostomy, although not truly a form of enterocystoplasty, is certainly one of the early attempts at bladder substitution. In the past, it was a popular method of continent urinary diversion, particularly in the management of bladder exstrophy. Although it is no longer the first choice for continent urinary diversion in the United States, it is still used successfully and as primary therapy in many parts of the world.

DPU: What are the problems most commonly associated with ureterosigmoidostomy?

TWH: The most alarming problems are the high rates of hyperchloremic, hypokalemic metabolic acidosis, ascending urinary tract infection, and pyelonephritis. We also have to recognize the significant increased rates of colon cancer at the junction where the urothelium joins the colonic mucosa. In 2005 adult patients who are living with ureterosigmoidostomy, or even patients who have had their ureterosigmoidostomies converted to another form of continent diversion, need regular colonoscopy to inspect the area where the anastomoses have been previously done.

DPU: Ureterosigmoidostomy aside, what else do we have to be concerned about after enterocystoplasty?

TWH: The terminal ileum and segments of the large bowel, such as the ascending colon, are the most commonly used components of the gastrointestinal tract for enterocystoplasty and continent urinary diversion.

DPU: What are the advantages and disadvantages of each?

TWH: The advantages of using ileum include the abundant amount of bowel, a predictable and abundant mesenteric blood supply, a good deal of compliance of the bowel segment, modest mucus production as compared to the colon, and less severely associated metabolic complications when compared to either stomach or colon.

DPU: What are the drawbacks of using ileum?

TWH: The ileum is not a suitable bowel segment to be used in certain situations and is contraindicated in a patient with a history of short-gut syndrome, inflammatory bowel disease, previous pelvic and abdominal radiation, and significant renal insufficiency. Although it is the most commonly utilized bowel segment for augmentation and continent diversion, ileal segments are associated with several limitations including the occasional development of significant hyperchloremic/hypokalemic metabolic acidosis, vitamin B12 deficiency, as well as both diarrhea and steatorrhea.

DPU: What about colocystoplasty? Would that be better?

TWH: Enterocystoplasty using colon is complicated by a whole set of anatomic and functional characteristics unique to large bowel. A shorter mesentery makes mobilization and reconfiguration of the large bowel more difficult and, in addition, colon is associated with a significantly higher degree of mucus formation.

DPU: Why does metabolic acidosis occur with the use of enterocystoplasty?

TWH: When gastrointestinal segments are used in the urinary tract there is a net absorption of ammonium (NH4+) which is a major contributor to the increased acid load, and metabolic acidosis. To a lesser extent, bicarbonate losses, which are caused by the use of bicarbonate to titrate endogenous and ingested acids and the inability of the kidneys to secrete acid can contribute to the acidosis. In patients with adequate renal function the kidneys are able to process the increased acid load and seldom do significant clinical consequences arise. Still, in approximately 50% of patients with ileal bladder replacement, a degree of metabolic acidosis can be noted and in more than 50% of the patients with colonic reservoirs there is a significant and measurable degree of hyperchloremic metabolic acidosis.

DPU: Do these metabolic derangements get better or worse over time?

TWH: There is some evidence that the absorptive properties of intestinal segments used in enterocystoplasty may decrease over time although this is not entirely clear. Certainly, histologic changes of intestinal mucosa do take place, including mucosal atrophy and decreased villous height. This has been implicated as a potential mechanism for reducing intestinal absorptive capacity. For patients who have had enterocystoplasty for a long time, acidosis is not typically severe. The clinical significance of minor degrees of acidosis has not been well elucidated although the majority of patients will have a measurable electrolyte abnormality such as increased serum chloride (Cl) and ammonium (NH4+) levels. When the acidosis is significant, symptoms include easy fatigability, anorexia, weight loss, polydipsia, and lethargy.

DPU: What is the treatment for this metabolic acidosis?

TWH: Primary treatment of chronic metabolic acidosis in the face of intestinal cystoplasty should be alkalinization with oral sodium bicarbonate, however, other oral alkalinizing agents can be used such as sodium citrate and citric acid solutions. These therapies are not well tolerated by most children as sodium bicarbonate produces a considerable amount of gas and the taste of sodium citrate can be described at best as unpalatable. The use of chlorpromazine or nicotinic acid may limit the degree of acidosis and decrease the need for alkalinizing agents, although they do not correct the acidosis alone. Both of these agents...
act through inhibiting the cyclic adenosine monophosphate (cAMP), and impeding chloride transport. These agents have significant side effects of their own and consequently their use is limited.

DPU: What about problems with potassium?
TWH: Low potassium levels seen in patients with continent urinary diversion commonly result from renal potassium wasting and chronic metabolic acidosis which causes intracellular potassium depletion. Ileal segments have a greater capacity for potassium reabsorption as compared to colon segments which may help attenuate the hypokalemia in patients with ileal augmentations and continent diversions made from ileum. Patients with continent colon urinary diversions and ureterosigmoidostomies have an increased risk for developing hypokalemia compared to the ileoneobladder. Severe depletion of potassium may result in flaccid paralysis and the treatment of hypokalemia consists of replacement of potassium in addition to correction of the acidosis with bicarbonate. Care must be taken during correction of the acidosis to monitor potassium levels closely as correction of the acidosis will result in an intracellular potassium shift which can lead to profound and dangerous hypokalemia.

DPU: What other metabolic problems can be seen?
TWH: Although hypocalcemia and hypomagnesemia can occur with urinary diversion, they are uncommon. Chronic metabolic acidosis results in the loss of calcium stores from bone as phosphates and sulfates are used to buffer these acids. Clinically significant hypocalcemia can result in symptoms including tetany, tremors, irritability, and in extreme cases, sudden death. The treatment is based on calcium repletion. Hypomagnesemia results from magnesium malabsorption, renal losses, and decreased renal tubular absorption secondary to acidosis. Symptoms are similar to those that occur with low calcium levels and treatment consists of exogenous magnesium replacement.

DPU: After colon and ileum, what are other alternatives for enterocystoplasty?
TWH: The jejunal syndrome is more commonly seen when proximal jejunum is used, the incidence is affected in direct relationship to the length of the jejunal segment employed. Bottom line: Don’t do it.

DPU: What about gastrocystoplasty?
TWH: The use of stomach for bladder substitution and augmentation is not as common today as it was 10 years ago. In certain specific instances, however, gastric segments can be a valuable adjunct to the more commonly used techniques. The metabolic benefits of gastrocystoplasty include intestinal sparing and the prevention of short-bowel syndrome, a decreased occurrence of hyperchloremic metabolic acidosis, and decreased mucus production, which translates into lower rates of both urine infection and stone formation within augmented bladders. Patients with renal insufficiency and chronic acidosis may benefit from inclusion of a gastric segment into their bladder substitution due to the stomach’s ability to secrete acid. The use of stomach in patients who require either continent urinary diversion or bladder augmentation, however, is not without its consequences.

DPU: What are the downsides of using a gastric segment in the urinary tract?
TWH: Fluid, potassium, and chloride losses may develop, resulting in severe dehydration and hypochloremic/hypokalemic metabolic acidosis. These metabolic abnormalities may precipitate clinical presentations ranging from lethargy and mental status changes to intractable seizures. In severe cases, respiratory compromise related to compensatory respiratory acidosis that develops in response to the metabolic alkalosis can be seen.

DPU: How can these problems be prevented?
TWH: Patients with urinary reconstruction, including gastric segments, must be instructed to maintain adequate hydration and salt intake to prevent clinically significant dehydration from developing. Acute gastrointestinal illness can precipitate severe metabolic alkalosis requiring hospitalization, particularly in patients with baseline renal insufficiency. When patients do present with symptoms, electrolyte and fluid repletion are primary treatment objectives, and normal saline infusion and potassium repletion typically correct the metabolic abnormalities. In patients with minimal alkalosis H2 blockers and anticholinergic therapy can be instituted. In severe cases of alkalosis not responsive to more standard therapy, omeprazole can be used to inhibit potassium-hydrogen (K+/ H+) ion exchange.

GASTROCYSTOPLASTY

ADVANTAGES
- NO MUCOUS / NO INFECTION
- EASY TO REIMPLANT
- NO METABOLIC ACIDOSIS

DISADVANTAGES
- HYPOCHLOREMIC ALKALOSIS
- HEMATURIA / DYSURIA SYNDROME
DPU: Are there any other complications of gastrocystoplasty?

TWH: A potentially painful complication of gastrocystoplasty is the hematuria/dysuria syndrome (HDS). This complex includes dysuria, genital skin irritation and excoriation as well as bladder spasms, suprapubic and/or urethral pain and gross hematuria. The etiology is likely related to chemical irritation of the urothelium when exposed to gastric acid. Treatment includes increased fluid intake, correction of the potassium abnormalities, the use of (H2) blockers, and anticholinergics. At times, it requires the removal of the gastric segment. Hematuria/dysuria syndrome can be a particular problem in sensate patients and careful consideration should be used before using stomach as part of the reconstruction in a sensate patient.

DPU: Do we have to be concerned about Vitamin B12 deficiency in patients who have undergone enterocystoplasty in childhood?

TWH: Using the terminal ileum in urinary diversion can result in several nutritional deficiencies and approximately 15cm of ileum proximal to the ileocecal junction should be spared if possible when using ileum for augmentation or diversion. Vitamin B12 deficiency is a well recognized abnormality that may arise with resection of the terminal ileum. Vitamin B12 is an essential vitamin that cannot be synthesized by the human body, and must be obtained from dietary sources. Deficiency of Vitamin B12 causes megaloblastic anemia and various neurologic consequences including peripheral neuropathy, optic atrophy, degenerative changes in the spinal cord involving the dorsal lateral columns, and dementia. Axonal degeneration is a late and irreversible manifestation of Vitamin B12 deficiency. The incidence of Vitamin B12 deficiency ranges from 3 to 20% when ileum is used in urinary diversion as reported in various series. Continent urinary diversion increases the risk mostly because of larger sections of ileum are needed and the ileocecal junction may be incorporated into the diversion.

DPU: How do we prevent Vitamin B12 deficiency?

TWH: Vitamin B12 deficiency can be prevented by beginning with an injection of 100µg of B12 monthly one year following surgery when patients have had more than 50cm of ileum removed during their urinary reconstruction.

DPU: What about steatorrhea?

TWH: Surgical resection of the terminal ileum can also result in fat malabsorption, altered bile salt reabsorption, and resultant decreased fat-soluble vitamin absorption. Removal of more than 100cm of ileum results in bile acid and lipid malabsorption, even in the presence of an intact terminal ileum and ileocecal valve. Bile acids are typically cycled at a constant rate, with approximately eight cycles of enterohepatic circulation occurring daily. On average 500mg of bile are excreted with the feces each day with the obligate deficit matched by hepatic bile acid synthesis. When fecal losses exceed hepatic production, fat malabsorption occurs. Resultant steatorrhea occurs with impaired fat absorption and, consequently, fat soluble vitamins are not absorbed adequately. The secretory diarrhea that results from bowel acid malabsorption can cause severe clinical irritation of the colon and results in excessive loss of both chloride and water. Symptomatic patients can be treated with oral cholestyramine and low-fat diet. Diarrhea secondary to the removal of the ileocecal valve can be managed with lomotil in an attempt to decrease intrinsic transit time of the feces to the colon. Long-term complications of fat malabsorption are not well defined, however, recent reports have found that patients with ileal orthotopic neobladders have persistent hypertriglyceridemia. The long-term clinical significance of this finding is not known.

DPU: What about the problem of bone loss and growth retardation in children who have had enterocystoplasty?

TWH: One of the most concerning areas in the use of enterocystoplasty in children is the potential impact on growth. There has been historical data repeated with long-term follow-up suggesting that intestinal cystoplasty may negatively impact growth and development. Most of these studies are old and were done in patients with myelodysplasia. While most of the patients in these studies do have growth retardation, it is unclear whether it is due to the primary disease or the urinary diversion. Most recent data, with confounding factors removed, suggest that intestinal cystoplasty is not associated with growth retardation. In one recent study looking at patients who had colocystoplasty in an effort to define the long-term metabolic effects and its impact on linear growth, the authors looked at two groups of patients in their series 1. One group had cystoplasty with cecum and ascending colon and the second group using sigmoid colon. Their conclusion was that all colonic cystoplasty is associated with a significant degree of long-term metabolic derangement and a high incidence of metabolic acidosis. They further concluded a higher degree of metabolic acidosis is seen in patients undergoing sigmoid cystoplasty compared to those undergoing either cecal or right colon cystoplasty. In addition, there were significant changes in linear growth among the sigmoid cystoplasty group but not in the cecal or ascending colon cystoplasty group suggesting that the impact of long-term metabolic acidosis may well play a significant role in children’s growth following enteroenterocystoplasty.

DPU: What about chronic bacteriuria, urinary tract infection, and calculus disease?

TWH: Bacteriuria and colonization of the urinary tract following enterocystoplasty is common particularly in patients requiring clean intermittent catheterization (CIC). In most series, symptomatic urine infection occurs between 15 and 20% of patients who have had enterocystoplasty and are on CIC. The incidence of urine infection particularly with urea-splitting organisms such as Klebsiella in combination with mucus production from the enterocystoplasty can lead to stone formation and chronic infection. Rates of reservoir calculi following either enterocystoplasty or continent urinary diversion range from 15 to 50%. Several factors may be contributory to stone formation.

**URETEROCYSTOPLASTY**

**ADVANTAGES**
- NO BOWEL INVOLVED
- NO MUCOUS PRODUCTION
- UROTHELIUM TO UROTHELIUM

**DISADVANTAGES**
- LIMITED AVAILABILITY (SO FAR)
i.e., urinary stasis, mucus production, and colonization with urea-splitting organisms. It is also interesting that stone formation is more common in patients who catheterize from the umbilicus down after continent urinary diversion than those who catheterize per urethra from the bottom up, implying that residual mucus is an inciting factor.

DPU: What is the management and prevention for calculus disease in association with bowel segments in the urinary tract?

TWH: The management of calculus disease in urinary diversion and augmentation is largely preventative. During the surgery, staples and non-absorbable sutures should never be used as they can facilitate stone formation. Postoperatively, patients should remain well hydrated and a regular program of bladder or pouch irrigation should be used. We have demonstrated through our series that an irrigation protocol can reduce the incidence of reservoir calculus disease from 40% to less than 10% in compliant patients.

DPU: What about the problem of spontaneous bladder perforation? How prevalent is that and what is the treatment?

TWH: Delayed spontaneous bladder perforation is a dangerous complication of enterocystoplasty. Patients typically present with abdominal pain and distention and occasionally present with fever, although a high index of suspicion is necessary for prompt diagnosis and treatment. Insensate patients are at greater risk and typically present later in the course of their problem. The cause of spontaneous perforation is unknown although several etiologies have been suggested including traumatic catheterization, bladder outlet obstruction, urinary retention, chronic infection, and chronic bowel wall ischemia secondary to chronic over-distention. Spontaneous perforation is seen in approximately 10% of patients undergoing enterocystoplasty. The incidence of perforation is probably highest in patients who have had ileocystoplasty versus collocystoplasty although this is not entirely clear. The management of perforation can often be conservative using catheter drainage, antiobiotic coverage and hydration, although it is not unusual for surgical exploration and repair to be required particularly in acute cases.

DPU: What about the formation of tumors following enterocystoplasty?

TWH: The risk of malignancy at the ureteral anastomosis following ureterosigmoidostomy is well documented. The risk of carcinogenesis in an isolated intestinal segment where feces and urine do not mix, however, is not as well defined. There have been many reports of adenocarcinoma and some transitional cell carcinoma developing after enterocystoplasty. To date, about 60 such tumors have been reported, half involving ileal segments and half involving colonic segments. Most of the tumors reported were adenocarcinomas although some transitional cell carcinomas have been reported as well. Most interestingly, in three patients reported very recently from Indiana University who had undergone enterocystoplasty, all developed transitional cell carcinomas and all three cancers were muscle invasive and originated in the native bladder in patients who were at minimal risk for bladder cancer. The investigators estimated a 1.2% prevalence of bladder cancer in patients with enterocystoplasty assuming a 10-year latency period for risk of cancer development.

DPU: What is your take home message, Dr. Hensle?

TWH: The use of gastrointestinal segments is a better alternative than having an external urinary drainage device; enterocystoplasty, however, is not a perfect solution. Complications and metabolic abnormalities associated with enterocystoplasty are often predictable and treatable, however, their development underscores the limitations of intestinal segments to substitute for urothelium. The complications are not limited to the genitourinary system and the use of bowel interposed into the urinary tract can also be associated with several gastrointestinal complications such as short-gut syndrome, B12 deficiency, and streatorrhea. Several more concerning complications such as renal deterioration, both bone and growth impairment, and the development of latent tumors, including adenocarcinomas and transitional cell carcinomas have yet to be completely defined. These potential late complications emphasize the importance of long-term follow-up and further clinical research into these incompletely defined entities. Because of the multiple complications that do arise from enterocystoplasty there has been considerable interest in developing techniques that avoid interposition of the gastrointestinal segments into the genitourinary tract. These include auto-augmentations, seromuscular enterocystoplasties, and ureterocystoplasty. Thus far, experience is limited and these techniques have not been proven to have widespread clinical application. Our own work in tissue expansion of the ureter as a source of additional urothelium continues and tissue engineering is a fertile topic that has developed over the last several years. Although wide spread clinical application has not yet been realized with tissue engineering, a good deal of progress has been made and this technology holds great promise for the future in terms of urinary diversion and augmentation.

2 Rink, et al: in press
I hope that the holidays are happy and healthy for you and your family. I am pleased to send along with these wishes our final issue of Dialogues for 2004. We are on schedule to produce six issues of Dialogues in 2005, and Editor Tony Caldamone has Dialogues on course, with a very successful future assured because of his management. Tony had the foresight to include international participation on the editorial board and has secured a long list of future guest editors.

By now, everyone is aware that the ABU has approved a Certificate of Added Qualification (CAQ) in pediatrics. The acceptance of a CAQ is a tremendous advancement for pediatric urology. It is the culmination of hard work by a number of urologists over many years. Most recently Gil Rushton has been working with the trustees of the ABU on behalf of the pediatric Coordinating Council. I realize the time was right and I do not want to take away anything from the work done by other leaders in pediatric urology, but much of the current success was directly related to the effort that Gil put into the certification process. His attention to detail and ability to communicate pushed the CAQ process over the top. This is a job well done by Gil and an important victory for pediatric urology. There is still a way to go before finalization of the CAQ and certificates are in hand, but there is “light at end…” The approval of the CAQ signals an important commitment that the pediatric Coordinating Council and the ABU made to ensure that pediatric urologists remain a significant component of organized urology and do not splinter from their parent organization as other pediatric surgical sub-specialties have. This is definitely a win for urology, for pediatrics, and most importantly, for children.

Make your reservations now for the annual meeting to be held May 21st at the San Antonio Marriott Riverwalk Hotel. Scientific Program Chair Warren Snodgrass has prepared a fantastic program that includes panels on Complex Re-operative Procedures in the Treatment of Hypospadias and Urodynamic Testing in Infants With Myelomeningocele; a state of the art presentation by Aviar Bracka on Alternative Views of Hypospadias Surgery; a point counter point on Surgical Management of Upper Tract Stones in Prepubertal Children; and a video forum on Advanced Injection Techniques for the Correction of Vesicoureteral Reflux and Urinary Incontinence. Don’t plan on resting during the lunch hour or you will miss a discussion on Pediatric Urology Fellowship Training, an important topic for all, particularly in light of the CAQ. The Meredith Campbell Lecture, The Courage to Succeed, will be given by Jackie N. Pflug. Ms. Pflug has been featured on the Oprah Show, Larry King Live, Good Morning America, and in People Magazine. This presentation documents her survival of a terror attack on an airliner, and will surely be an inspirational experience that you won’t want to miss and one that I expect you will not soon forget. The annual meeting will also mark the first time that continuing medical education credit can be received for attendance. Local Arrangements Chair Elizabeth Yerkes has planned an end to the day’s activities with a casual Texas-style night of fine food and entertainment at the Buckhorn Saloon and museum, all within a short walking distance from area hotels.

The SPU continues to gain momentum and strength. The recent accomplishments are in large part due to the secretarial time and effort put in by Marc Cendron and the administrative help received from Aurelie Alger and the staff of PRRI. They have really taken on an incredible amount of work without hesitation. Their hard work is appreciated.

I want to hear about your comments and concerns regarding the SPU. Feel free to contact me or anyone on the Executive Committee.

In closing, I send all of you greetings and best wishes for the New Year.
It is with great pride and pleasure that the Society for Pediatric Urology (SPU) announces the resumption of publication of Dialogues in Pediatric Urology. For twenty-five years Dialogues served the pediatric urology field as a valuable resource. The SPU debuted the Spring Edition of Dialogues in Pediatric Urology, and finally the enormous changes that the Society has undergone through the efforts of Aurelie Alger, Executive Director. But, hold on, more is happening: the SPU web-site is undergoing a major face-lift, an updated manpower survey is being circulated and the final touches of an outstanding educational program for the spring meeting in San Antonio are being made. It is crucial for all US based pediatric urologists to fill out the ManPower survey. The current uncertainty with regards to job availability and number of pediatric urologists to train demand that we get a sense of the job market. The survey, while not perfect, should give us a sense of the current needs. So do not procrastinate, fill out the survey and send it back ASAP. It will be tabulated by an independent organization and its results will be presented by Doug Husmann in San Antonio.

Finally, let me stress that the leadership at the SPU is committed to improve and grow the Society. Please do not hesitate to contact me if you have suggestions, ideas or feedback.

Marc Cendron, M.D.
INSIDE THIS ISSUE......

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