

Urinary Diversion: Core Curriculum 2021

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Urinary diversion after cystectomy has been a historical standard for the treatment of numerous benign and malignant diseases of the bladder. Since the first published description in the early 1900s, improvements in surgical technique and a better understanding of the metabolic sequelae postoperatively have greatly enhanced patient outcomes. Both continent and incontinent diversions are available to patients after cystectomy. In appropriately selected patients, orthotopic neobladder reconstruction can offer preservation of body image and continence, and continent cutaneous diversions represent a reasonable alternative. Conduit diversion, which remains the most commonly performed diversion technique, is ideal for patients who would benefit from a less morbid surgical procedure that negates the need for self-catheterization. This installment of the Core Curriculum in Nephrology outlines numerous aspects of urinary diversion, in which a multidisciplinary approach to postoperative management at the intersection of nephrology and urology is required to effectively optimize patient outcomes. This article includes a discussion of the various reconstructive options after cystectomy as well as a comprehensive review of frequently encountered short-term and long-term metabolic abnormalities associated with altered electrolyte and acid-base homeostasis.

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Am J Kidney Dis.
78(2):293-304. Published
online May 8, 2021.

doi: [10.1053/
j.ajkd.2020.12.023](https://doi.org/10.1053/j.ajkd.2020.12.023)

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Introduction

Urinary diversion after cystectomy has revolutionized the treatment paradigm of both benign and malignant diseases of the urinary tract since its conception over 150 years ago. A normally functioning bladder, in the simplest sense, is a highly compliant reservoir for the storage of urine at low pressures. When the physiologic utility of the bladder has been compromised in the setting of neoplastic, functional, or anatomic aberration, cystectomy with urinary diversion is often indicated with the goal of preserving kidney function and patient survival.

Procedurally, urinary diversion has evolved considerably over time from simple diversion of the ureters to the skin to near functional restoration by means of orthotopic reconstruction using autologous intestinal segments. With proper counseling and patient selection, these refinements in surgical technique have enabled patients to better personalize their care by selecting the type of diversion most likely to result in low postoperative morbidity and favorable quality of life.

Despite these innovations, postoperative complications after urinary diversion can be substantial, ranging from 56% within the first 30 days to 90% after 30 days. Patients often experience one or more metabolic, functional, and psychological changes that can significantly impair quality of life.

This Core Curriculum installment discusses various reconstructive options after cystectomy, patient selection criteria, postoperative complications, functional outcomes,

and metabolic abnormalities associated with urinary diversion.

Urinary Diversion: Selection of Patient and Surgical Management

Indications for Urinary Diversion

Malignant Disease

Bladder cancer, specifically of urothelial origin, is the sixth most commonly diagnosed noncutaneous malignancy in the United States, with an estimated 81,400 new cases and 17,980 deaths in 2020 alone. At the time of initial diagnosis, 20% to 30% of patients will present with muscle invasive bladder cancer (MIBC). Additionally, 20% of patients who initially present with non-muscle invasive disease will progress to MIBC despite bladder-preserving treatment strategies. Without definitive therapy, MIBC carries a poor prognosis, with a 5-year cancer-specific mortality rate of 86%.

Radical cystectomy with urinary diversion is the historical standard of care for nonmetastatic MIBC, irrespective of histologic variant. Given that roughly 50% of patients will experience progression to metastatic disease with radical cystectomy alone, particularly if surgery is delayed by more than 12 weeks after their diagnosis, current guidelines support administration of cisplatin-based neoadjuvant chemotherapy, with published literature suggesting an absolute 10-year overall survival benefit of 6% in patients with a good pathological response. Although indications for radical cystectomy vary based on patient age and comorbidities,

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

this multimodal treatment strategy has resulted in pelvic recurrence rates as low as 4% in patients without nodal metastases at the time of surgery.

Benign Disease

Urinary diversion for benign conditions is not commonly performed in the United States. Currently, it exists merely as a last-resort treatment modality in patients with severe lower urinary tract symptoms that do not respond to medical treatment or less invasive surgical therapy. Guidelines issued by the American Urological Association endorse urinary diversion for refractory non-neurogenic overactive bladder as a fourth-line management strategy only.

Data regarding urinary diversion for benign disease are sparse and primarily limited to single-institution series. Recent literature, however, suggests that the most common indication for benign diversion is neurogenic bladder (multiple sclerosis, Parkinson's disease, spinal cord injury, and spina bifida) followed by radiation cystitis, interstitial cystitis, and recurrent fistulous defects. Interestingly, for the majority of cases in the United States, cystectomy is not commonly performed at the time of urinary diversion. Although there exists no evidence-based consensus as to whether or not to perform a concomitant cystectomy, it appears that the risk of residual pain and carcinoma due to a retained bladder must be weighed against the risk of increased procedural morbidity.

Additional Readings

- Brown ET, Osborn D, Mock S, et al. Perioperative complications of conduit urinary diversion with concomitant cystectomy for benign indications: a population-based analysis. *Neurourol Urodyn*. 2017;36:1411-1416.
- Brown ET, Osborn D, Mock S, et al. Temporal trends in conduit urinary diversion with concomitant cystectomy for benign indications: a population-based analysis. *Urology* 2016;98:70-74. **★ESSENTIAL READING**
- Funt SA, Rosenberg JE. Systemic, perioperative management of muscle-invasive bladder cancer and future horizons. *Nat Rev Clin Oncol*. 2017;14:221-234. **★ESSENTIAL READING**
- Martini A, Sfakianos JP, Renstrom-Koskela L, et al. The natural history of untreated muscle-invasive bladder cancer. *BJU Int*. 2020;125:270-275.
- Osborn DJ, Dmochowski RR, Kaufman MR, et al. Cystectomy with urinary diversion for benign disease: indications and outcomes. *Urology* 2014;83:1433-1437.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7-30.

Selection of Urinary Diversion

No ideal method of urinary diversion currently exists, but advances in urinary tract reconstruction have led to 2 general categories: incontinent diversion, which includes the urinary conduit, and continent diversion, which comprises both the cutaneous reservoir and orthotopic neobladder (Box 1). Overall, large variation exists in the use of urinary diversion techniques. Some higher-volume centers of excellence report using orthotopic neobladder

Box 1. Summary of Types of Urinary Diversion With Notable Distinguishing Features

Urinary Conduit

- Most commonly performed surgical urinary diversion
- Incontinent—requires urostomy appliance at all times
- Features an abdominal wall stoma

Orthotopic Neobladder

- Higher surgical complexity limits use to high-volume centers
- Features a continent urinary reservoir
- Voiding initiated by Valsalva

Continent Cutaneous Urinary Diversion

- Least commonly performed diversion
- Features a continent urinary reservoir
- Voiding necessitates ability to self-catheterize an abdominal wall stoma

diversion in as many as 90% of radical cystectomy cases whereas several population-based datasets alternatively report 90% use of urinary conduits. The reasons behind this large variation are undoubtedly multifactorial, and considerations regarding oncologic, functional, and quality of life outcomes must be considered. Of note, the presence of a rare histologic variant of bladder cancer, including squamous cell and adenocarcinoma, do not appear to influence the choice of urinary diversion.

Of significant importance during preoperative planning is a thorough assessment of baseline kidney function. Most patients will experience a decline in long-term kidney function after urinary diversion, and multiple factors are believed to play a role, including advancing age, patient comorbidities such as diabetes and hypertension, urinary tract obstruction, and use of nephrotoxic chemotherapeutic agents. The intestinal segment to be used as a conduit or pouch for diversion will be bathed in excreted urine and a patient's ability to accommodate the increased reabsorption of urinary solutes is paramount in the prevention of life-threatening metabolic abnormalities. In a study of 1,600 patients who underwent radical cystectomy with either incontinent (76%) or continent (24%) urinary diversion, Eisenberg et al demonstrated that 73% of the overall cohort experienced a decline in estimated glomerular filtration rate (eGFR) of >10 mL/min/1.73 m², but the type of urinary diversion did not independently predict GFR decline. In addition, the strongest predictor of GFR decline, aside from hypertension, was preoperative eGFR. In general, among the other factors considered, patients with a GFR >40 mL/min/1.73 m² and a serum creatinine <2.0 mg/dL are deemed safe to undergo either continent or incontinent diversion. Other considerations will be discussed separately.

Additional Readings

- Eisenberg MS, Thompson RH, Frank I, et al. Long-term renal function outcomes after radical cystectomy. *J Urol*. 2014;191:619-625.

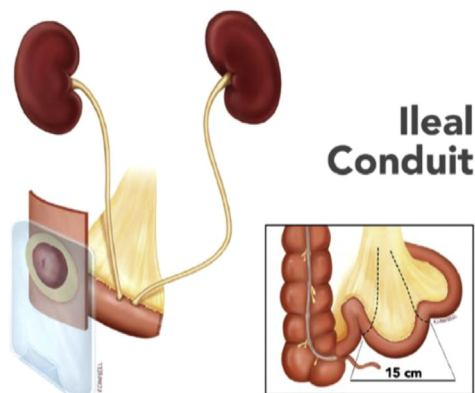


Figure 1. Schematic illustration of an ileal conduit. The ureters drain into the conduit, a well-vascularized segment of terminal ileum, which is then brought out through the abdominal wall as a stoma for continuous drainage. Image ©2019 Elsevier Inc; reproduced with permission of the copyright holder from Shergill et al 2019 (*Curr Probl Diagn Radiol*, <https://doi.org/10.1067/j.cpradiol.2018.02.001>).

➤ Faraj KS, Mi L, Eversman S, et al. The effect of urinary diversion on long-term kidney function after cystectomy. *Urol Oncol*. 2020;38(10):796.e15-796.e21. ★**ESSENTIAL READING**

Incontinent Urinary Diversion

Urinary Conduit

Multiple intestinal segments have been used in conduit urinary diversion. However, the ileal conduit is the most commonly performed, accounting for 33% to 84% of all urinary diversions worldwide, and remains the procedure of choice for patients with contraindications to continent diversions. This technique, first described in the literature in 1950 by Eugene Bricker, has been enhanced and widely adopted due to refinements in surgical technique and perioperative care leading to enhanced quality of life.

The hallmark of a urinary conduit (as well as a continent cutaneous diversion) is the creation of a stoma, which is the protrusion of bowel through the anterior abdominal wall to allow for excretion of urine (Fig 1). To construct a urinary conduit, an isolated section of well-vascularized bowel is selected intraoperatively, after which the proximal end is sewn into a blind pouch while the distal end protrudes through the anterior abdominal wall. The ureters are sutured into small holes created in either the proximal or lateral walls of the conduit (ureteroenteric anastomosis) to allow for the excretion of urine through the abdominal wall stoma.

Urinary Conduit Postoperative Care and Surgical Complications

Up to two-thirds of patients will require assistance with their urostomy. Although the need for physical dexterity is not as crucial compared to orthotopic reconstruction, patients' ability to adequately care for their urostomy appliance is paramount.

The overall incidence of kidney function decline after urinary diversion has been reported in up to 74% of cases. In a study of over 1,000 patients who underwent radical cystectomy with ileal conduit urinary diversion who were assessed postoperatively for a median duration of 15 years, new onset of chronic kidney disease (CKD) was reported in 19% of the overall cohort, and 15% developed urolithiasis. In addition, 10% developed strictures at the ureteroenteric anastomosis, a well-known long-term complication after conduit urinary diversion that occurs in up to 14% of patients. The precise etiology of this anastomotic stricture is unclear, although poor surgical technique leading to compromised blood flow to the distal ureter can result in postoperative urine leakage and peri-ureteral fibrosis. Although some studies have suggested that ureteral stent placement across the ureteroenteric anastomosis may decrease the rate of urine leak, current level 1 evidence does not support an association between ureteral stenting and long-term stricture rate.

Additional Reading

➤ Shimko MS, Tollefson MK, Umbreit EC, et al. Long-term complications of conduit urinary diversion. *J Urol*. 2011;185:562-567.

Continent Diversion

Orthotopic Neobladder

Orthotopic neobladder reconstruction, which has revolutionized the management of urinary diversion after radical cystectomy, consists of a segment of detubularized bowel that is surgically modified to anatomically and functionally approximate the bladder (Fig 2). The notion of using bowel as an internal urinary reservoir with a direct anastomosis to the native urethra is not a novel concept: it was first pioneered in the early 20th century. Although this technique has gained substantial popularity over the past several decades, the changing epidemiology of MIBC may be influencing its actual use. Interestingly, despite the apparent benefits of an orthotopic neobladder—obviating the need for an abdominal wall stoma, and resulting in improved body image and the ability to void voluntarily—the rate of orthotopic diversion has been declining over the past decade. The reasons behind this trend are not entirely known, but patient-specific factors such as advanced age, obesity, and comorbidity likely play a large role. In addition, given the procedural complexity of the required reconstruction, surgeon-specific factors such as low individual case volume and consolidation of orthotopic neobladder reconstruction to higher-volume tertiary care centers are surely driving the trend.

The voiding mechanism in patients with an orthotopic neobladder consists of initiation of the Valsalva maneuver, followed by relaxation of the external urethral sphincter. In light of this, orthotopic neobladder reconstruction generally strives to replicate 4

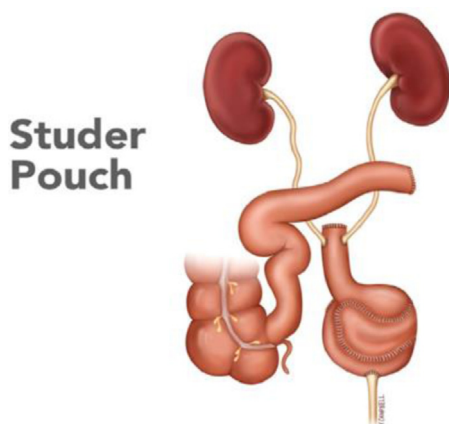


Figure 2. Schematic illustration of an orthotopic neobladder. One variation, known as the Studer pouch, is created from terminal ileum. The neobladder is then anastomosed to the native urethra for preservation of volitional voiding. Image ©2019 Elsevier Inc; reproduced with permission of the copyright holder from Shergill et al 2019 (*Curr Probl Diagn Radiol*, <https://doi.org/10.1067/j.cpradiol.2018.02.001>).

characteristics of a normal lower urinary tract: a compliant reservoir with adequate capacity (between 300 and 500 mL) and low filling pressures, an antirefluxing mechanism to prevent upper urinary tract dilation, preservation of an intact external urethral sphincter to achieve continence, and maintenance of an unobstructed urethra. The specific surgical techniques for construction of the orthotopic neobladder are beyond the scope of this review, but most surgeons prefer to use a segment of ileum. Based on the Law of Laplace (Pressure = Tension / Radius), intraluminal pressure is inversely related to the radius of a spherical reservoir. To achieve a neobladder with ideal urodynamic characteristics, bowel is folded into a spherical shape to maximize volume while detubularization aids in the preservation of continence and protection of the upper tracts by inhibiting the frequency and amplitude of peristaltic contractions.

Orthotopic Neobladder Patient Selection

Patient selection is key for favorable outcomes after orthotopic neobladder urinary diversion. Compared with urinary conduit diversions, orthotopic diversions may require a period of self-catheterization postoperatively, thereby requiring both mental competency and physical dexterity to facilitate sufficient neobladder training. Although studies have demonstrated that chronological age is associated with a higher likelihood of postoperative complications, functional status, motivation to avoid a stoma, and the ability to tolerate a longer and more surgically demanding procedure appear to better predict favorable outcomes. Absolute contraindications of orthotopic neobladder diversion include a positive urethral

margin, poor kidney function (GFR < 40 mL/min/1.73 m² or serum creatinine > 2.0 mg/dL), inability to perform self-intermittent catheterization due to neurologic or physical decline, hepatic insufficiency, or severe urethral strictures. Other important factors that affect the integrity of the small bowel include a history of inflammatory bowel disease or pelvic radiation (Box 2).

Orthotopic Neobladder Postoperative Care and Surgical Complications

Compared with conduit urinary diversion, orthotopic neobladder diversion carries a unique set of challenges that must be addressed in the immediate postoperative period. The bowel mucosa used for the creation of the reservoir can secrete >30 g of mucus per day. Until the mucosal epithelium begins to atrophy and lose its secretory function, there is a risk of mucus buildup and subsequent urinary retention. To prevent pouch overdistention, patients will have a prolonged need for urethral catheterization.

Patients with an orthotopic neobladder may continue to experience complications many years after their procedures. The most common late complications of orthotopic diversion include voiding dysfunction, urinary tract infections, and ureteral strictures. Although the incidence of febrile urinary tract infection is similar across all urinary diversion techniques, the rates of asymptomatic bacteriuria can be as high as 78% in patients with an orthotopic neobladder; this is likely because around 10% of men and 50% of women will require self-catheterization to adequately empty their reservoir. The risk of ureteral stricture development is primarily a function of surgical anastomosis technique and appears to be similar to that of ileal conduit diversions.

Functional outcomes are best optimized with careful patient selection. The goal of orthotopic neobladder reconstruction is to provide patients with the ability to maintain continence and volitional voiding. As such, patients must be motivated and willing to adhere to a strict rehabilitation pathway. In addition to a rigid timed-voiding schedule to gradually increase reservoir compliance, emerging evidence has supported the

Box 2. Absolute and Relative Contraindications for Orthotopic Neobladder Urinary Diversion

Absolute Contraindications

- Positive urethral margins
- Chronic kidney disease (serum creatinine > 1.7-2.2 mg/dL or estimated creatinine clearance < 35-40 mL/min)
- Inability to perform self-catheterization due to physical, neurological, or mental impairment

Relative Contraindications

- Plan for postoperative radiation
- Chronic inflammatory or malignant bowel disease
- Recurrent urethral strictures

benefit of pelvic floor physical therapy to prevent incontinence. The development of voiding dysfunction in this population can vary, although pooled observations support the notion that daytime continence improves over the first 6 to 12 months postoperatively. In one study of 200 patients who underwent an radical cystectomy with orthotopic neobladder reconstruction, daytime and nighttime continence rates at 10 years were 92% and 70%, respectively. Of this cohort, 23% developed reservoir outlet obstruction, most commonly due to mucosal prolapse or anastomotic stricture. Most of these complications can be managed endourologically, but these findings stress the importance of a patient's ability to self-catheterize.

Additional Reading

➤ Pietzak EJ, Donahue TF, Bochner BH. Male neobladder. *Urol Clin North Am.* 2018;45:37-48. ★**ESSENTIAL READING**

Continent Cutaneous Diversion

Continent cutaneous urinary diversion was first developed by Richard Gilchrist in the 1950s alongside Bricker's urinary conduit. Given the less demanding surgical prowess required for construction of an ileal conduit, the continent cutaneous reservoir was largely abandoned until interest was renewed in the 1980s.

With the increased adoption of orthotopic neobladder reconstruction, continent cutaneous urinary diversion is no longer commonly performed. However, this option is ideal for patients who desire continence, are capable of intermittent self-catheterization, and would otherwise qualify for orthotopic neobladder reconstruction but whose urethra cannot be incorporated due to pre-existing benign strictures or malignant disease. While unique among urinary diversion techniques, continent cutaneous urinary diversion has a number of characteristics common to both ileal conduit and orthotopic diversion. Similar to orthotopic neobladder reconstruction, continent cutaneous urinary diversion is a continent diversion that uses an isolated section of well-vascularized bowel to create an internalized low-pressure reservoir for the storage of urine. As with urinary conduit diversion, a stoma is fashioned on the anterior abdominal wall. In contrast to both of the aforementioned techniques, the reservoir created in continent cutaneous urinary diversion may be ectopically placed and uses a continent catheterizable stoma that negates the need for a bulky external urostomy appliance.

Numerous variations exist in performing continent cutaneous urinary diversion and are beyond the scope of this review. The Indiana pouch, however, is the most commonly used technique in reservoir construction (Fig 3). Briefly, a segment of bowel involving the entire right hemicolon and terminal ileum are isolated with its blood supply. The colonic segment is detubularized and folded into a spherical pouch, while the

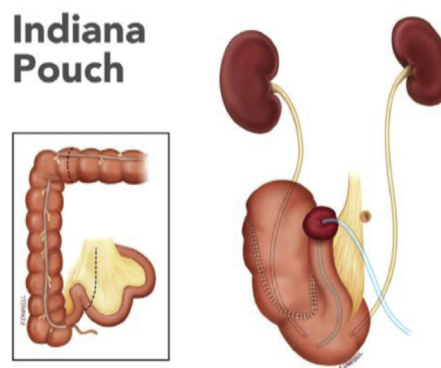


Figure 3. Schematic illustration of an Indiana pouch, the most common variation of a continent cutaneous urinary reservoir. The ureters drain into the reservoir, which is constructed from the right hemicolon, while the terminal ileum is brought out through the abdominal wall as a catheterizable stoma. Image ©2019 Elsevier Inc; reproduced with permission of the copyright holder from Shergill et al 2019 (*Curr Probl Diagn Radiol*, <https://doi.org/10.1067/j.cpradiol.2018.02.001>).

terminal ileum is passed through the abdominal wall for the creation of a cutaneous stoma. In using this configuration, the terminal ileum functions as a catheterizable channel, while an intact ileocecal valve provides a natural continence mechanism.

Continent Cutaneous Diversion Postoperative Care and Surgical Complications

As with orthotopic neobladder diversion, continent cutaneous urinary diversion is subject to a similar set of postoperative challenges that must be addressed immediately after surgery. To prevent pouch overdistention from excess mucus plugging, patients require close monitoring of urine output and frequent catheter irrigation. At the authors' institution, interval catheter irrigation begins on postoperative day 1 and is continued until reservoir integrity is confirmed by a fluoroscopic pouchogram 4 weeks later.

Short-term overall complications after continent cutaneous urinary diversion have been shown to occur more frequently compared with ileal conduit and orthotopic neobladder diversion. In a study of 209 patients who underwent radical cystectomy followed by either ileal conduit, orthotopic neobladder, or continent cutaneous urinary diversion, 72%, 88%, and 76% of patients, respectively, experienced at least 1 complication within 90 days. Urinary tract infections were also significantly more common in continent cutaneous urinary diversion patients, which may be related to the inherent need for frequent self-catheterization. The rate of general long-term complications—including kidney function decline and ureteroenteric strictures—appears similar to orthotopic neobladder reconstruction. However, one study noted a 15% rate of stomal stenosis at 41 months, of which the majority required surgical revision.

Additional Reading

- Nazmy M, Yuh B, Kawachi M, et al. Early and late complications of robot-assisted radical cystectomy: a standardized analysis by urinary diversion type. *J Urol*. 2014;191:681-687. ★**ESSENTIAL READING**

Metabolic Complications of Urinary Diversion

Case: A 69-year-old man was found to have microscopic hematuria during routine urinalysis. After referral to urology, cystoscopic evaluation of his lower urinary tract revealed a 3-cm posterior bladder wall mass. Pathology and staging were ultimately notable for nonmetastatic muscle invasive urothelial cell carcinoma. He underwent a 3-month course of cisplatin-based neoadjuvant chemotherapy that he tolerated well, although he experienced moderate bone marrow suppression and paresthesias. Upon completion, he underwent radical cystectomy, regional lymphadenopathy, and urinary diversion. After surgery he was doing well and following up regularly with urology and medical oncology for cancer surveillance.

Several months later, the patient was eventually referred to the general nephrology clinic for evaluation of progressively worsening kidney function and metabolic acidemia. He denies use of any nonsteroidal anti-inflammatory medications. Laboratory values revealed the following: serum creatinine, 1.4 mg/dL (preoperative serum creatinine was 0.9 mg/dL, corresponding to a GFR as estimated by the MDRD Study equation of 83 mL/min/1.73 m²); serum sodium, 142 mEq/L; serum chloride, 112 mEq/L; serum bicarbonate, 19 mmol/L; serum urea nitrogen, 32 mg/dL; serum potassium, 5.4 mEq/L; serum magnesium, 1.6 mg/dL; serum calcium, 8.6 mg/dL; and serum albumin, 3.8 g/dL. The liver function tests, including aminotransferase levels, were within the reference range.

Question 1: Given this clinical scenario, what is/are the possible etiologies of this patient's hyperkalemia?

- Decreased kidney function
- Reduced urinary ammonium excretion
- Reduced colonic bicarbonate loss
- Pancreatic bicarbonate losses
- Cisplatin toxicity resulting in hyperkalemic acidemia

Question 2: Which one of the following statements regarding this patient's clinical scenario is true?

- Measurement of urine electrolytes and calculation of anion gap are a reliable method for the diagnosis of this patient's hyperchloremic acidemia.
- Administration of nicotinic acid and chlorpromazine is an adequate treatment regimen.
- Citrate or bicarbonate-based buffer supplementation can effectively treat both acidemia and hyperkalemia in patients with an ileal conduit urinary diversion.
- This clinical scenario is more common with diversions using gastric segment.

For the answers to the questions, see the following text.

The fundamental goal of urinary diversion after cystectomy is the prevention of decreases in kidney function, preservation of residual kidney function, and the creation

of a urinary reservoir that can anatomically and functionally emulate the urinary bladder in terms of storage, continence, and urination/voiding. The success of urinary diversion depends not only on perioperative planning and surgical technique but also on a comprehensive understanding of the associated short-term and long-term anatomical and physiological complications. In this part of the review, we will focus on various metabolic complications of urinary diversion (Fig 4).

Physiology of Metabolic Complications of Urinary Diversion

Metabolic abnormalities that are frequently encountered in patients after urinary diversion are due primarily to the incorporation of a segment of bowel that is not physiologically intended to endure the fluid composition of urine, as well a reduction in bowel surface area resulting in malabsorption.

Diarrhea is a frequent manifestation of malabsorption secondary to intestinal resection. Chronic diarrhea (>6 months' duration) has been reported in up to 11% of patients after ileal resection and 23% of patients after ileocecal resection. Depending on the type of diversion technique, the mechanism of diarrhea may differ. The terminal portion of the ileum is required for bile salt reabsorption and therefore assists in fat-soluble vitamin absorption. Jones and McDougal showed that the interposition of intestinal segments in the urinary track did change the composition of the urointestinal track depending on the segment of bowel used for interposition. As such, resection of the terminal ileum may cause increased transit of bile salts into the colon, which can lead to diarrhea, steatorrhea, and fat-soluble vitamin deficiencies due to impaired fat absorption. In addition, the ileocecal valve at the junction of the terminal ileum and cecum acts as an "ileal brake" that prevents the rapid transit of intestinal contents into the colon. Surgical resection of the ileocecal valve may also contribute to rapid intestinal transit and the development of chronic diarrhea.

The remaining ileum is susceptible to bacterial overgrowth and can also contribute to diarrhea. The small intestinal cystic fibrosis transmembrane receptor channel (CFTR) is responsible for transcellular brush border chloride secretion and concomitant paracellular sodium secretion. The activation of calcium-dependent cyclic adenosine monophosphate (cAMP) is required for this mechanism. If the terminal ileum is used for creation of a urinary conduit, intraluminal amphiphilic bile salts and acids may remain unabsorbed, which can lead to secretory diarrhea by means of cAMP-dependent, CFTR-mediated chloride and sodium excretion. Diarrhea can be treated with volume repletion if required, bile acid sequestrants (cholestyramine), increased dietary fiber, and antidiarrheal agents such as loperamide.

Vitamin B₁₂ deficiency can often be a late sign of malabsorption after gastric or small bowel resection. The stomach is responsible for intrinsic factor release that is required for vitamin B₁₂ absorption in the terminal

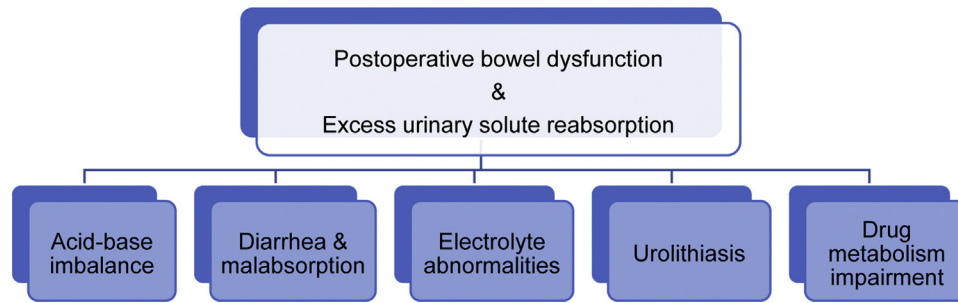


Figure 4. Possible sequelae of postoperative bowel dysfunction and excess urinary solute reabsorption after urinary diversion.

ileum. Therefore, malfunction of either bowel segment can lead to vitamin B₁₂ malabsorption and subsequent deficiency leading to megaloblastic anemia and peripheral neuropathy.

Additional Readings

- Bricker EM. Bladder substitution after pelvic evisceration. *Surg Clin North Am.* 1950;30:1511-1521.
- Field M. Intestinal ion transport and the pathophysiology of diarrhea. *J Clin Invest.* 2003;111:931-943. **★ESSENTIAL READING**
- Jones JS, McDougal WS. Alterations in bile following urinary intestinal diversion. *J Urol.* 1992;148:1288-1289.
- Terai A, Okada Y, Shichiri Y, et al. Vitamin B12 deficiency in patients with urinary intestinal diversion. *Int J Urol.* 1997;4:21-25.
- Van der Aa F, Joniau S, Van Den Branden M, et al. Metabolic changes after urinary diversion. *Adv Urol.* 2011;2011:764325.

Acid-Base Disorders

Physiology of Acid-Base Disorders

The mechanisms contributing to the development of electrolyte abnormalities after urinary diversion are not well understood. Although animal models have been used in the study of urinary conduits and bowel-derived neobladders for more than 150 years, most were conducted before the identification of several novel solute transport mechanisms in the renal and intestinal epithelium.

It is now understood that bowel epithelium is composed of a single layer of cells separated by leaky intercellular junctions; this arrangement allows for isotonic absorption of water and solutes, leading to equilibration of urinary contents. Solute absorption in bowel is sodium dependent via the sodium/hydrogen exchanger 3 (NHE3), which in turn is responsible for providing protons for the absorption of several organic oligopeptides, sugars, and amino acids. Several of these transport mechanisms are shown in Figure 5.

The low pH of urine in which the intestinal segment is exposed to may lead to a reduction in the gradient required for proton exchange via the intestinal NHE3 antiporter, and therefore result in reduced sodium-dependent solute absorption. Previous studies have hypothesized that the intestinal NHE3 antiporter plays a role in the generation of acid-base abnormalities in patients with a urinary neobladder. However, the discovery of

chloride-bicarbonate exchangers, specifically PAT-1 (encoded by SLC26A6) and DRA (encoded by SLC26A3) in small intestinal epithelium, as well as ammonia

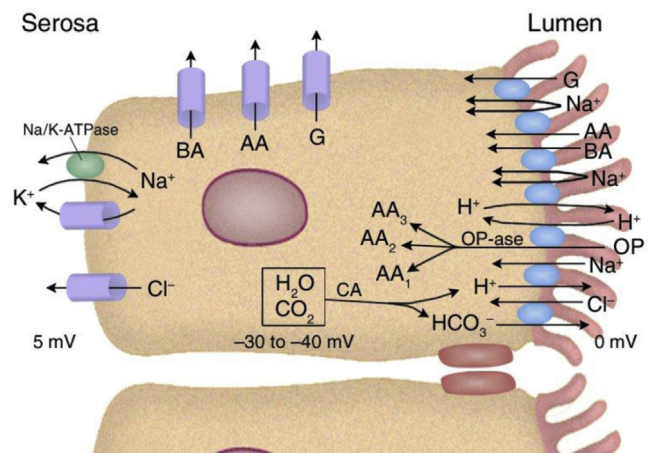


Figure 5. Ileal absorptive cell. Several brush border transporters are responsible for the coupling of ion influxes (Na⁺ and, in one instance, H⁺) with the coinflux or exchange of other ions or organic solutes. Alternatively, basolateral membrane carriers facilitate the diffusion of organic solutes and are not coupled to the movement of other ions. The adenosine triphosphatase sodium/potassium pump (Na⁺/K⁺-ATPase) in the basolateral membrane uses energy derived from adenosine triphosphate hydrolysis to drive Na⁺ extrusion and K⁺ uptake (3:2 stoichiometry) against their electrochemical gradients. K⁺ and Cl⁻ channels in the basolateral membrane open in response to cellular swelling and elevations in intracellular calcium. Some of the cellular H⁺ and HCO₃⁻ extruded in exchange for Na⁺ and Cl⁻ is provided through the action of carbonic anhydrase (CA). Additional HCO₃⁻ may enter the cell through the basolateral membrane sodium/hydrogen exchanger 1 or the Na⁺/HCO₃⁻ cotransporter (not shown). The cell electric potential is 30-40 mV negative relative to the lumen, providing both an electric and chemical driving force for Na⁺ entry via Na⁺-organic solute cotransport. Abbreviations: AA, amino acid (there are actually several amino acid carriers); BA, bile acid anion; Cl⁻, chloride anion; G, glucose or galactose; HCO₃⁻, bicarbonate; K⁺, potassium cation; Na⁺, sodium cation; OP, oligopeptide; OPase, oligopeptidase (almost all oligopeptides entering the cell intact are quickly hydrolyzed). Image ©2003 American Society for Clinical Investigation; reproduced with the permission of the copyright holder from Field 2003 (*J Clin Invest*, <https://doi.org/10.1172/jci18326>).

transporters RHBG and RHCG in colonic epithelium, may change our mechanistic understanding of how acid-base abnormalities develop. It is currently theorized that ammonia excretion may occur in the kidney, while ammonia reabsorption and bicarbonate excretion may occur in the bowel in patients with a conduit or orthotopic neobladder. These mechanisms could help explain the chronic acid load in patients after urinary diversion, but further studies are required to understand these pathophysiological mechanisms.

Reduced sodium absorption can result in diarrhea, mild volume depletion, and proton retention that further potentiates an acidotic state, while reduced nutrient absorption can lead to malnutrition. Volume depletion and acidemia may also result in a high aldosterone state, which can contribute to renal potassium loss.

In their animal model, Koch et al demonstrated that a hyperchloremic metabolic acidosis with a lowering of total serum carbon dioxide could be induced in 0.5 months after vesico-cecostomy in male rats. In addition, reabsorption of creatinine, urea, and inulin in female dogs after insertion of an ileal segment between the ureter and bladder was noted to be flow dependent, leading to a modestly higher than baseline concentration of these solutes. Given the increased reabsorption of uremic solutes, the traditional eGFR equations may underestimate true GFR. Therefore, a 24-hour urine collection from which serum urea nitrogen concentration and creatinine clearance is calculated should be used as an alternative.

Histological abnormalities in the mucosa of intestinal segments have been reported after long-term exposure to urine. Villous atrophy and pseudocrypt formation are common findings in ileal segments. Mucus-producing goblet cells, whose normal physiologic function is to create a physical barrier between the gut microbiota and epithelium, are also commonly decreased in number and secretory function. Although solute transport mechanisms may be altered in the long term, the ability to generate a hyperchloremic metabolic acidosis is retained by ileal and colonic segments over time. Despite these adaptations, the composition of urine voided from a ureteroenteric conduit is altered by intestinal solute and water transport mechanisms. The passive epithelial transport of water equilibrates the osmolality of urine with serum. In addition, changes in final pH and electrolyte content are often altered by the absorption of ammonia and other inorganic solutes. These mechanisms can render voided urine inaccurate for assessment of solute clearance and renal tubular function using tests such as urine anion and osmolar gap and water deprivation test.

Additional Readings

- Grocela JA, McDougal WS. Ammonium transport in the intestine chronically exposed to urine: is it reduced over time? *Urology*. 1999;54:373-376.
- Koch MO, McDougal WS. Chlorpromazine: adjuvant therapy for the metabolic derangements created by urinary diversion through intestinal segments. *J Urol*. 1985;134:165-169. **★ESSENTIAL READING**
- Koch MO, McDougal WS. Determination of renal function following urinary diversion through intestinal segments. *J Urol*. 1985;133:517-520.
- Koch MO, McDougal WS. Nicotinic acid: treatment for the hyperchloremic acidosis following urinary diversion through intestinal segments. *J Urol*. 1985;134:162-164.
- Koch MO, McDougal WS. The pathophysiology of hyperchloremic metabolic acidosis after urinary diversion through intestinal segments. *Surgery*. 1985;98:561-570.
- McDougal WS, Stampfer DS, Kirley S, et al. Intestinal ammonium transport by ammonium and hydrogen exchange. *J Am Coll Surg*. 1995;181:241-248. **★ESSENTIAL READING**
- Philipson BM, Kock NG, Jagenburg R, et al. Functional and structural studies of ileal reservoirs used for continent urostomy and ileostomy. *Gut*. 1983;24:392-398.
- Xia W, Yu Q, Riederer B. The distinct roles of anion transporters Slc26a3 (DRA) and Slc26a6 (PAT-1) in fluid and electrolyte absorption in the murine small intestine. *Eur J Physiol*. 2014;466(8):1541-1556.

Clinical Context of Acid-Base Disorders

Observational studies have suggested that some degree of metabolic acidemia after urinary diversion is associated with both small and large bowel conduits. The mechanism and degree of acidemia, however, largely depends on the bowel segment used for creation of the conduit. Gastric neobladders, for example, although no longer commonly used, can be associated with hypokalemia, hypochloremia, and metabolic alkalosis, likely due to secretion of these ions by the gastric epithelium. If kidney function and volume status are normal, this metabolic alkalosis is corrected by urinary bicarbonate excretion. Alternatively, patients with decreased kidney function or hypovolemia can develop a secondary hyperaldosteronism, which can lead to maintenance and propagation of this disorder.

Reduced stomach volume can occasionally result in overdistension and intractable vomiting, further contributing to this acid-base abnormality via loss of protons, potassium, and chloride. In mild cases, antiemetics can be used to reduce loss of upper gastrointestinal secretions to prevent further proton loss, and proton secretion can be lowered using H₂ blockers and proton pump inhibitors. Postoperatively, gastric neobladders will continue to secrete gastrin (in addition to gastrin secretion from the gastroplasty segment) in response to distension. Gastrin levels > 120 ng/L have been shown to correlate incrementally with serum bicarbonate levels in patients with gastroplasty. As such, patients should be made aware of this complication and instructed to avoid overdistension of the gastric neobladder segment by timed voiding.

Severe cases of metabolic alkalosis can manifest in the form of respiratory depression due to hypercarbia, which can progress to lethargy, seizures, and ventricular arrhythmias. The treatment of this life-threatening abnormality should be focused on airway protection, treatment

of the underlying cause, and correction of electrolyte abnormalities. Intravenous normal saline with potassium chloride can treat chloride responsive metabolic alkalemia; if the patient's blood pressure is normal, a potassium-sparing diuretic like amiloride (5-10 mg), triamterene (50-100 mg), or spironolactone (12.5-50 mg) may be used cautiously to reduce the metabolic effects of secondary hyperaldosteronism. Lysine or arginine hydrochloride infusion should be avoided as these can cause unpredictable hyperkalemia in volume-depleted patients. Acetazolamide should also be avoided for treatment of alkalemia in such circumstances as it can lead to further hypokalemia. If persistent severe metabolic alkalemia continues despite the aforementioned measures, the gastric neobladder may need to be removed and revised with an alternative method of urinary diversion.

When jejunum is used for urinary tract reconstruction (particularly proximal jejunum), 25% of patients will develop a postoperative electrolyte disorder syndrome characterized by volume depletion, hyponatremia, hyperkalemia, and metabolic acidemia. The underlying mechanisms are multifactorial, but include a reduced absorptive surface area of available jejunum, which leads to an initial volume depletion with secondary aldosteronism. This high-aldosterone state alters the composition of urine to contain low concentrations of sodium and high concentrations of potassium and ammonium or protons. Ultimately, this creates a favorable gradient for sodium loss and potassium/acid gain through the leaky jejunal brush border epithelium. This "jejunal conduit syndrome" can be rapidly progressive and refractory to treatment if not identified and treated early or even preemptively. Symptoms are usually related to volume depletion, hyponatremia, and hyperkalemia. The usual clinical presentation is that of lethargy, intractable vomiting, muscle weakness, dehydration, and occasional fevers. Parenteral hyperalimentation is known to worsen these metabolic abnormalities. The reason for this is unknown, but increased metabolic solute burden and osmotic diuresis resulting in polyuria could be a cause.

The severity of jejunal conduit syndrome depends on the location and length of the jejunum used; it is more common with the use of proximal long-segment jejunal conduits. Severe abnormalities are encountered in <4% of cases if short jejunal segments are used.

The treatment of jejunal conduit syndrome is primarily preventive, and consists of careful surgical planning to avoid using long bowel loops for conduit creation. Perioperatively, volume depletion should be treated with intravenous normal saline and bicarbonate supplementation (a normal sodium bicarbonate solution can be used for this purpose). Parenteral hyperalimentation should be avoided; however, patients requiring this postoperatively for bowel rest should be administered formulations with a low azotemic and solute load and carefully monitored.

Long-term management of patients with jejunal conduits includes the administration of loop diuretics along

with oral sodium supplements (in the form of sodium chloride or bicarbonate) for the treatment of both hyperkalemia and hyponatremia. Sodium bicarbonate is effervescent and may increase bowel output, so patients should be made aware of this complication before administration. Novel potassium binders like patiomer and sodium zirconium cyclosilicate have not been studied for the treatment of hyperkalemia after urinary diversion. However, these medications have proven to be safe and effective for the treatment of hyperkalemia in other clinical scenarios associated with CKD, heart failure, and use of renin-angiotensin blockers. These potassium binders can be used in cases of refractory hyperkalemia along with dietary modifications, diuretics, and sodium supplementation. Sodium polystyrene sulfonate, particularly when administered with sorbitol, has been associated with bowel necrosis in the immediate postoperative period and should be avoided.

The metabolic abnormality most frequently associated with ileal and colonic conduits is a hyperchloremic metabolic acidosis. Studies from the 1970s reported the incidence of metabolic acidemia around 68% to 70%; more contemporary studies place the incidence at around 25%, with roughly 4% of patients requiring hospitalization for treatment. This metabolic abnormality is more frequently observed in ureterosigmoid diversions and Mainz pouch (ileocecal bladder augmentation) reconstruction when compared with ileal segment use, although most patients with ileal or colonic diversions do have some degree of long-standing acidemia and hyperchloremia. The mechanism of hyperchloremic metabolic acidemia seems to be related to ammonium absorption by the NHE3 exchanger, along with chloride gain via chloride and bicarbonate exchange.

The most commonly reported clinical manifestations associated with ileal and large bowel conduits are often related to the patient's type of metabolic derangement. Acidemia can manifest as anorexia, weight loss, lethargy, sarcopenia, and asthenia. Hyponatremia can result from the development of free water loss and dehydration, which can further propagate osmotic diarrhea, polydipsia, and lethargy.

The treatment of metabolic acidemia is alkali supplementation with oral sodium bicarbonate (650 mg tablets or baking soda, titrated to a serum total carbon dioxide level of 21-23 mEq/L), although these can cause bloating. Citrate supplements can be used as an alternative (sodium citrate, potassium citrate, and citric acid solution), although the taste can be offensive and some patients may experience diarrhea. Patients with decreased kidney function may develop a mild hyperkalemia with potassium-based supplements (potassium bicarbonate or potassium citrate). For cases of acute worsening of chronic moderate acidemia where high doses of buffer supplementation are not tolerated or sodium load is unacceptable, the chloride exchange inhibitors chlorpromazine or nicotinic acid may be used. Long-term use of chlorpromazine can cause extrapyramidal

side effects like tardive dyskinesia, and nicotinic acid should be avoided in patients with liver disease and peptic ulcer disease, as both these conditions can be exacerbated. Additionally, nicotinic acid is also known to cause flushing, dermatitis, and diplopia, which can limit its tolerability. As such, these alternative therapies should be limited to short-term “rescue” measures under careful supervision.

Increased ammonium reabsorption is also of concern in patients after urinary diversion with ileal or large bowel conduit reconstruction, which can lead to encephalopathy in specific patient populations. Hyperammonemic encephalopathy is usually serious in patients with underlying significant liver dysfunction but has also been documented in patients with normal liver function as determined by serum enzyme levels. Whether patients included in these studies had subtle abnormalities in liver function or alternative reasons for encephalopathy remains unknown. However, when the hyperammonemia is severe it should be treated with drainage of the urinary conduit. Enteric ammonia load can be reduced by adhering to a low-protein diet, and supplementation with oral neomycin and/or lactulose can decrease ammonia production and increase excretion, respectively. In severe cases of refractory hyperammonemic coma, use of intravenous arginine glutamate (50 g in 1 L of 5% dextrose solution) has been described. Arginine complexes with ammonia to produce glutamine and reduces serum ammonia levels. Alternately, hemodialysis can be used in patients who have acute kidney injury or CKD.

Patients with ileal and colonic diversions can also develop hypokalemia. This complication is also commonly associated with ureterosigmoidostomies (no longer commonly performed), most likely because urinary potassium can be reclaimed by the ileum but not by the colonic segments. In one study, 30% of total body potassium depletion was reported in ureterocolonic diversions while no significant reduction was noted in the ileal conduits. Potassium depletion is frequently associated with metabolic acidemia in both ileal and colonic diversions, and these metabolic derangements must be treated concomitantly. Monotherapy with sodium bicarbonate supplementation can rapidly increase renal potassium excretion and intracellular potassium shift, and lead to life-threatening hypokalemia—which can manifest as lethargy, severe muscle weakness with occasionally flaccid paralysis, and cardiac arrhythmias.

Similar to electrolytes and endogenous solutes, therapeutic drugs and xenobiotics, particularly ones that are renally excreted in their metabolically active form, can be reabsorbed by the intestinal conduit and cause potential toxicities. Phenytoin and methotrexate toxicity have been well described in previous studies in the setting of ileal conduit urinary diversions. In patients with a continent urinary diversion, the time of re-exposure to the drug can be prolonged. It is prudent to adhere to careful therapeutic drug level monitoring, and strong consideration should be given to continuous drainage of continent reservoirs in patients receiving adjuvant chemotherapy. Similarly, in

patients with diabetes who have uncontrolled hyperglycemia, urinary glucose can be reabsorbed by the intestinal epithelium and further exacerbate the hyperglycemic and hyperosmolar state. The absence of glycosuria in such cases again makes dipstick urinary glucose an unreliable metric for the renal threshold of glucose absorption.

Returning to question 1, although our current understanding of urinary electrolyte handling in a patient with a urinary conduit is not well developed, impaired urinary ammonia excretion has been shown in animal models as well as human studies, which makes (b) the best answer. Although kidney failure may cause acidemia and this patient does have acidemia, it is out of proportion to his kidney function. Colonic bicarbonate losses when increased, not reduced, cause acidemia. Pancreatic fistulas can be a complication of chronic pancreatitis but are not usually associated with urinary conduits. Cisplatin exposure can be associated with tubulopathies, including a Fanconi-like renal tubular acidosis, hypomagnesemia, salt wasting syndrome, and event distal renal tubular acidosis, but hyperkalemic renal tubular acidosis is not a usual presentation of cisplatin nephrotoxicity.

Considering question 2, as discussed, within a conduit/neobladder, urine undergoes significant ion exchange that renders it unreliable to aid in the diagnosis of an acid-base abnormality. Use of gastric segments can cause a severe metabolic alkalosis; as such, their use is falling out of favor. Alkali supplementation in the form of citrate or bicarbonate salts is effective in the treatment of hyperkalemia and acidemia; thus, the best answer is (c). Neurolepts and nicotinic acid should be reserved for severe refractory cases for a short duration of time.

Additional Readings

- Bonnheim DC, Petrelli NJ, Sternberg A, et al. The pathophysiology of the jejunal conduit syndrome and its exacerbation by parenteral hyperalimentation. *J Surg Oncol*. 1984;26:172-175.
 - Fontaine E, Barthelemy Y, Houlgatte A, et al. Twenty-year experience with jejunal conduits. *Urology*. 1997;50:207-213.
 - Golimbu M, Morales P. Jejunal conduits: technique and complications. *J Urol*. 1975;113:787-795.
 - Gosalbez R, Jr., Woodard JR, Broecker BH, et al. Metabolic complications of the use of stomach for urinary reconstruction. *J Urol*. 1993;150:710-712.
 - Klein EA, Montie JE, Montague DK, et al. Jejunal conduit urinary diversion. *J Urol*. 1986;135:244-246.
 - Koff SA. Mechanism of electrolyte imbalance following urointestinal anastomosis. *Urology*. 1975;5:109-114.
 - Perez-Fidalgo JA, Chirivella Gonzalez I, Gunthner S, et al. Hyperammonaemic encephalopathy, possible complication after urinary diversion in radical cystectomy. Review of the literature with regard to a clinical case. Article in Spanish. *Actas Urol Esp*. 2007;31:394-399.
 - Tanrikut C, McDougal WS. Acid-base and electrolyte disorders after urinary diversion. *World J Urol*. 2004;22:168-171.
- ★**ESSENTIAL READING**
- Wintner A, Dahl DM. vol. 3 12th ed. Use of intestinal segments in urinary diversion. In: Partin AW, Dmochowski RR, Kavoussi LR, Peters CA, eds. *Campbell-Walsh-Wein Urology*. 12th ed. Elsevier; 2021;3:3160-3205. ★**ESSENTIAL READING**

Urolithiasis and Disorders of Bone Mineralization

Case, continued: *Sodium bicarbonate therapy with 650 mg tablets twice per day was started for this patient. A renal ultrasound was completed, which demonstrated 2 discrete 5-mm nonobstructive calculi in the right lower pole.*

Question 3: What of the following statements regarding urolithiasis in the setting of urinary diversion is true?

- After ileal conduit urinary diversion, the risk of urolithiasis is 1% to 2%.
- The most common types of urinary stones associated ileal conduit urinary diversions are composed of calcium oxalate and uric acid.
- The most effective strategies to prevent the formation of urinary calculi include the treatment of chronic acidemia and meticulous urinary hygiene.
- Routine monitoring for stone formation with 24-hour urine collections and imaging should be offered to all patients after urinary diversion.

Case, continted: *The patient does well over the next 6 months. At his routine follow-up visit, he has no significant concerns other than occasional diarrhea. He has been visiting appropriately with urology and medical oncology. Physical examination is unremarkable.*

Question 4: What additional investigations and/or interventions should be offered to this patient at this time?

- Three-site dual-energy X-ray absorptiometry scan, vitamin D levels, and daily multivitamin supplementation
- Serum ferritin, vitamin B₁₂, and testosterone levels
- Urinalysis and urine culture
- Fecal fat analysis and administration of cholestyramine

For the answers to the questions, see the following text.

Bone mineralization defects, commonly reported in patients after urinary diversion, result when the complex interplay of bone mineralization, apposition, and turnover becomes deranged. Bone biopsy and histomorphometric studies have demonstrated that vitamin D deficiency or resistance can lead to ineffective mineralization of osteoid seams. Alternatively, chronic metabolic acidemia results in reduced bone mineral apposition, which is defined as the linear rate of new bone deposition, demineralization of preformed bone, and the prevention new bone mineralization. In turn, excess calcium released from the process of demineralization is excreted in the urine and can increase the risk of nephrolithiasis. Previous studies have supported the use of alkalinizing agents, as even a mild degree of acidemia may cause significant osteomalacia. Bivalent anions, particularly sulfates, are avidly absorbed by the intestine. As serum sulfate concentrations increase, urinary sulfate excretion increases as well, and may in turn lead to an increase in urinary divalent cation loss, resulting in hypercalciuria and hypermagnesuria, which can potentially lead to stone formation. This scenario may also lead to severe

hypomagnesemia, which can reduce parathyroid hormone (PTH) release and PTH insensitivity. Additionally, intestinal fat malabsorption can lead to fat-soluble vitamin D deficiency, which further exacerbates the bone demineralization. In the presence of CKD, reduced activation of vitamin D may result in resistance to supplementation with inactive vitamin D. Activated vitamin D analogues such as calcitriol should be used in these circumstances, which may also help with secondary hyperparathyroidism of kidney disease.

Bone mineralization defects have a detrimental effect on skeletal bone growth and development, particularly in the pediatric population, as well as an increased susceptibility to fractures. The most common clinical presentation is fatigue, proximal myopathy (likely due to calcium, magnesium, and phosphate depletion), and arthralgias of weight-bearing joints.

Further workup may reveal laboratory abnormalities, including hypomagnesemia, mild hypocalcemia, hypophosphatemia, and a variable degree of metabolic acidosis and decreased kidney function. Vitamin D levels may be low with a high alkaline phosphatase level. Depending on the degree of decreased kidney function and levels of vitamin D and calcium, PTH levels can be variable.

Treatment of mineral-bone disease is focused on vitamin D repletion. If laboratory derangements and skeletal issues persist despite vitamin D repletion, or in the setting of decreased kidney function with a high PTH, activated vitamin D₃ (1- α -hydroxycholecalciferol) should be given. Additionally, care should be taken while treating acidemia, as alkali supplementation can lower serum levels of ionized calcium. Magnesium and calcium should be supplemented concomitantly to avoid this complication. Early detection or surveillance with bone density scanning followed by timely treatment of bone demineralization with physical therapy can improve patient outcomes.

Urolithiasis has been reported with both colonic (4%) and ileal conduits (10%-12%). In patients with a cecal reservoir, there is a 20% incidence of pouch stone formation. The most common types of calculi associated with urinary conduits are calcium, magnesium, and ammonium phosphate stones. Risk factors for recurrent stone formation include a persistent metabolic acidosis, pre-existing pyelonephritis, and recurrent urinary tract infections with urea-splitting organisms. Additionally, urinary tract obstruction or retention, or the presence of foreign bodies such as staples, may also serve as a nidus for stone formation. As such, surgical technique, urinary infection prevention, and careful treatment of underlying metabolic acidosis can reduce the risk of urolithiasis. Although there exists no evidence-based data to support the use of routine monitoring for urinary calculi, high-risk patients with a history of urolithiasis may benefit from some form of surveillance.

Returning to question 3, as noted previously, the risk of urolithiasis varies from 4% to 20% depending on the type of conduit. The most common type of stone in patients after urinary diversion are triple-phosphate stones (magnesium ammonium phosphate

stones), which are caused by the colonization of urea-splitting bacteria in the urinary tract. These stones can be prevented by meticulous genitourinary hygiene to prevent urinary tract infections or asymptomatic bacterial colonization. Treatment of acidemia can prevent bone turnover but should be used carefully. The best answer is therefore (c). Although urolithiasis is relatively common, neither “screening” 24-hour urine collections or imaging are a cost-effective strategy to reduce the incidence of new kidney stones.

Regarding question 4, malabsorption, nutritional deficiencies, and bone mineralization defects can persist after urinary diversion. Careful screening and timely intervention can prevent these long-term complications, therefore the best answer is (a). Although vitamin B₁₂ deficiency is a known complication of bowel resection, screening should be carried out with a thorough neurological examination and a complete blood count first. If a patient exhibits symptoms of intractable large-volume diarrhea or urinary tract infection, a further workup may be warranted.

Additional Readings

- Agus ZS. Hypomagnesemia. *J Am Soc Nephrol*. 1999;10:1616-1622.
- Dretler SP. The pathogenesis of urinary tract calculi occurring after ileal conduit diversion. I. Clinical study. II. Conduit study. 3. Prevention. *J Urol*. 1973;109:204-209.

- McDougal WS, Koch MO. Effect of sulfate on calcium and magnesium homeostasis following urinary diversion. *Kidney Int*. 1989;35:105-115. **★ESSENTIAL READING**
- Richards P, Chamberlain MJ, Wrong OM. Treatment of osteomalacia of renal tubular acidosis by sodium bicarbonate alone. *Lancet*. 1972;2:994-997.
- Siklos P, Davie M, Jung RT, et al. Osteomalacia in ureterosigmoidostomy: healing by correction of the acidosis. *Br J Urol*. 1980;52:61-62.

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Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received May 26, 2020, in response to an invitation from the journal. Evaluated by 2 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form December 29, 2020.