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High Output Ileostomy

Evidence Based Medicine Guideline

Primary Author: Leila Becirevic, PharmD
Co-Authors: Kara Birrer, PharmD; Samuel Effoe, PharmD
Editor: Michael L. Cheatham, MD, Chadwick P. Smith, MD
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SUMMARY
Ileostomy can be a component of surgical treatment for various gastrointestinal conditions. Loss of the fluid absorptive capacity of the colon results in increased fluid and electrolyte losses, which causes a state of relative fluid depletion. High ileostomy output is typically a failure of adaptation or a post-adaptive process. When a high-output ileostomy (output ≥ 1500 mL / 24 hours) is present, potential causes must be considered and treated as appropriate. Additional management may include replacement of fluid and electrolyte losses, pharmacological interventions, and nutritional support.

RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **Patients with high ileostomy output will benefit from supplemental electrolytes, replacement of intestinal losses, and medications that target high output.**
- **Level 3**
  - **Initiate treatment when ileostomy output exceeds 1000 mL / 24 hours to slow gastrointestinal transit, reduce gastric acid secretions, and prevent progression to high-output.**
  - **Cholestyramine is indicated for treatment of choleretic diarrhea in patients with limited ileal resection (< 100 cm) and colon-in-continuity.**

INTRODUCTION

An estimated 100,000 surgical cases annually result in the creation of a stoma, of which approximately 40,000 are ileostomies (1). Given the truncation of the gastrointestinal (GI) tract and loss of the colon, ileocecal valve, and "ileal brake," ileostomy patients are at high risk for impaired gastrointestinal sodium and water absorption (2). Such alterations can lead to serious complications such as electrolyte derangements, dehydration, and acute kidney injury (AKI). Though the definition of high-ileostomy output is debatable, it is typically recognized that a total ileostomy output exceeding 1.5 L per day has the potential to lead to such complications (3,4). An estimated 20-30% of ileostomy patients experience high-output in the early postoperative period which imparts increases in morbidity, healthcare resource utilization, and length of inpatient stay (5-7). A retrospective study of 57 patients performed across three Orlando Health sites evaluated prescribing practices for the management of adult patients with high-output ileostomies. 56% of patients had a diagnosis of malnutrition, 44% developed AKI, and 96% experienced electrolyte abnormalities. Hospital readmission rates for these patients were 19% at 30 days, 28% at 60 days, and 33% at 90 days. Only 58% of patients were on medications to control ileostomy output at discharge. This study demonstrated a high incidence of complications associated with high-output ileostomies.

PATHOPHYSIOLOGY

Under normal circumstances, approximately 9-10 L of fluid, consisting of both oral intake and gastrointestinal secretions, are absorbed in the small and large intestine each day. The jejunum absorbs approximately 6 L and the

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Supported by multiple, prospective randomized clinical trials or strong prospective, non-randomized evidence if randomized testing is inappropriate.
- **Level 2:** Supported by prospective data or a preponderance of strong retrospective evidence.
- **Level 3:** Supported by retrospective data or expert opinion.

ileum 2.5 L, leaving approximately 1-1.5 L of fluid to enter the colon each day. Almost all of this fluid, and the electrolytes it contains, is reabsorbed in the colon, leaving an estimated 100 mL of excreted feces daily. Diversion of stool at the level of the ileocecal valve would be expected to produce approximately 1-1.5 L of stool output per day through the newly established ileostomy (8,9). Immediately after recovery from surgery, observed ileostomy output matches normal colonic fluid transport of 1-1.5 L per day (9). The output decreases over the following days to weeks as the distal intestinal mucosa adapts over time.

In addition to loss of absorptive surface, loss of the “ileal break” mechanism, with substantial ileal resection, likely contributes to poor adaptation (10). The ileum aids in reabsorption by providing a “braking” mechanism in which small intestine transit time is slowed through a neurohormonal process after meal consumption. Combined with the delayed emptying of intestinal contents into the colon by the ileocecal valve, this mechanism ultimately leads to enhanced nutrient and hydration absorption within the ileum (11). Loss of this mechanism following resection and creation of an ileostomy can lead to faster small bowel transit times and increased fluid losses proportional to the amount of ileum resected. Studies have shown that when greater than 100 cm of ileum is resected, bile salt reabsorption is decreased leading to steatorrhea and fat malabsorption (12). Multiple factors can therefore influence the development of high ileostomy output and adaptation can take weeks to months.

The process of intestinal adaptation following surgical resection is a compensatory mechanism which involves mucosal hypertrophy and hyperplasia and modification of gut-specific hormone levels (i.e., growth hormone, glucagon-like peptide-2, insulin-like growth factor, and epidermal growth factor) (9). Though there is not a consensus definition of what constitutes a “high-output” ileostomy, the proposed definition is greater than 1.5 L of daily output which is likely to lead to complications such as dehydration, electrolyte abnormalities, AKI, and eventually possible malnutrition (13,14).

LITERATURE REVIEW

Antimotility Agents

Antimotility agents exert their effects on opioid receptors which are widely distributed in the GI tract, delaying GI transit time and reducing intestinal secretions (15). The first-line agents within this class include loperamide and diphenoxylate. Systemic opioids, including codeine and tincture of opium, are often used when patients have failed to respond to first-line agents due to their risk of non-GI-related adverse effects which limit their overall use.

Loperamide

Loperamide is often used as a first-line agent in the treatment of high output ileostomies. It exhibits limited oral bioavailability and poor penetration across the blood-brain barrier making it an effective antidiarrheal with minimal adverse effects (15). There have been several small studies evaluating the use of loperamide for high-output ileostomies showing an improvement in output, however results varied across individual patients. One study conducted by King et al. compared codeine to loperamide in patients with increased ileostomy output and found that both drugs significantly decreased the daily output and water content of ileostomy fluid, but daily losses of sodium and potassium as well as adverse effects were fewer with loperamide (16). A study by Stevens et al. evaluated a single 6 mg dose of loperamide on stoma output in 22 patients of which 18 had ileostomies (17). Mean stoma output was reduced by 45% ($p=0.0001$) and there were no adverse events reported.

Diphenoxylate

Diphenoxylate is available as a combination product with atropine which is used as an abuse deterrent given that high doses of diphenoxylate may produce systemic effects such as euphoria and sedation. Newton tested the effects of codeine, diphenoxylate-atropine, and Isogel in 20 patients with ileostomies (18). Five patients received two tablets of 2.5 mg diphenoxylate-0.025 mg atropine three times daily. The use of diphenoxylate-atropine was associated with a small, nonsignificant decrease in total ileostomy output (difference -57 g; p=ns) and ileostomy output of water (difference -55 g; p=ns), but a significant decrease in ileostomy output of sodium (difference -8 mM; $p < 0.05$) and potassium (difference -0.4 mM; $p < 0.05$).

Codeine

Codeine is metabolized to morphine by CYP2D6. CYP2D6 mutations are common across several different ethnic populations and the effects of these mutations can result in either increased enzymatic activity, leading to increased risk of adverse effects, or decreased enzymatic activity, resulting in decreased efficacy of the drug. For this reason, codeine has become less commonly used than other systemic opioids. Newton

also evaluated codeine's efficacy on ileostomy output and found a significant decrease in total ileostomy output (difference -236 g; $p < 0.05$) and ileostomy output of water (difference -237 g; $p < 0.05$), sodium (difference -32 mM; $p < 0.05$), and potassium (difference -2.7 mM; $p < 0.05$) (18).

Tincture of Opium

Tincture of opium is another systemic opioid used to treat diarrhea and high ileostomy output. The CLARIFY trial, a prospective, multicenter, observational study of patients with diarrhea not relieved by loperamide, included patients with high-output ileostomies (defined as output exceeding 2000 mL per day) (19). Ileostomy output decreased from an average of 2.1 L to 1.3 L by day 14 of treatment. This study also found that tolerance for the antidiarrheal effect does not occur, as is often seen with the analgesic effect of opioids, and there was no dependence observed after discontinuation.

Antisecretory Drugs

Since ingested foods and liquids are diluted by digestive juices, agents that reduce secretions from the stomach, pancreas, and liver can reduce ileostomy volume (20). Commonly used drugs include proton pump inhibitors, histamine-2 receptor antagonists (H2RAs), and the somatostatin analog octreotide.

Proton Pump Inhibitors

Jeppesen et al. conducted a randomized, double-blind, crossover study to evaluate the effect of omeprazole and ranitidine on intestinal output in patients with short bowel syndrome (21). Omeprazole 40 mg twice daily for five days increased median intestinal wet weight absorption compared to placebo (difference 0.78 kg/day) and to ranitidine (difference 0.17 kg/day) ($p < 0.03$). Nightingale et al. evaluated the effect of omeprazole in 15 patients with short bowel syndrome and found a significant decrease in output compared to baseline (22).

Histamine-2 Receptor Antagonists

Two RCTs and two within-patient controlled studies evaluating ranitidine and cimetidine found that both agents had a significant effect on ileostomy output reduction (21,23-25). The first was a randomized trial discussed previously by Jeppesen et al. that compared the effects of omeprazole, ranitidine, and placebo on intestinal output in patients with short bowel syndrome (21). Ranitidine was dosed intravenously at 150 mg twice daily and resulted in a 0.46 kg/day reduction in intestinal wet weight absorption compared to placebo ($p=0.03$). Another randomized, double-blind, crossover study was conducted by Aly et al. evaluating the effect of cimetidine 400 mg daily on diarrheal volume and fecal sodium in 10 patients with Crohn's disease and diarrhea following extensive small bowel resection (23). The authors found that cimetidine significantly reduced diarrheal volumes by a mean value of 22% ($p < 0.05$) and fecal sodium by 27% ($p < 0.05$). A third study by Kato et al. evaluated the effect of intravenous cimetidine in five cancer patients with short bowel syndrome after massive small bowel resection (24). Patients were initiated on cimetidine 500 mg/m^2/day in addition to TPN. The authors found a reduction in output of 28% to 64% in each case. This study utilized a randomized block method for their statistical analysis and found a significant decrease in stool fluid excretion ($p = 0.0001$). Lastly, a within-patient controlled study by Jacobsen et al. evaluated the effect of intravenous cimetidine 400 mg four times daily in eight patients with high-output jejunostomies, defined as greater than two liters per 24 hours (25). Baseline ostomy output was 2133 to 8500 g per 24 hours with a median reduction of 499 g per 24 hours after treatment ($p < 0.01$). The authors concluded that cimetidine may be considered as an antidiarrheal agent in patients with high output jejunostomies.

Somatostatin (analog)

Somatostatin and octreotide reduce ileostomy output through their ability to decrease salivary, gastric, and pancreaticobiliary secretions, slow small bowel transit, and delay gastric emptying (20). Nubiola-Calonge et al. conducted a randomized, blind crossover trial on 14 patients with postoperative small bowel fistula (26). Patients were randomized to two days of octreotide, followed by two days of placebo (group 1) or vice versa (group 2), after which all patients were treated with octreotide until the fistula closed or operation was necessary. In group 1, mean fistula output was increased from 228 mL/24 hr on day two of octreotide to 497 mL/24 hr when treatment with octreotide was interrupted by placebo ($p=0.014$). In group 2, output decreased from 828 mL/24 hr on day two of placebo to 246 mL/24 hr after two days on octreotide ($p<0.01$). In 11 of the 14 patients, fistulas closed spontaneously after an average of 4.5 days of continuous treatment with octreotide. Kusuhara et al. conducted a randomized, placebo-controlled trial of 12 patients with ileostomies constructed 60 cm proximal to the terminal ileum following total proctocolectomy (27). Patients

were randomized to either octreotide 100 mcg subcutaneously three times daily or placebo for 5 days after a baseline 5-day period with no treatment. This study found that octreotide reduced the daily ileostomy output from 997 g to 736 g ($p < 0.05$) with no serious adverse effects reported. Scott et al. conducted a double-blind, randomized trial of 19 patients with postoperative enterocutaneous fistula (28). Patients were randomized to receive either octreotide 100 mcg subcutaneously three times daily or placebo for 12 days. Unlike the Nubiola-Calonge study, the authors of this trial did not find a significant difference in fistula output between the two groups nor did they find an increase in the rate of spontaneous fistula closure with octreotide. Sancho et al. examined the effect of octreotide 100 mcg subcutaneously every 8 hours compared to placebo in 31 patients with postoperative gastrointestinal or pancreatic fistula within 8 days of fistula onset (29). All patients received parenteral nutrition. The average reduction in output was similar between octreotide and placebo at 24 hr (66% vs. 68%, p=0.9), 48 hr (60% vs. 57%, p=0.8), and 72 hr (62% vs. 66%, p=0.9). Fistula closure was observed in 8 of 14 fistulas treated with octreotide compared to 6 of 17 patients who received placebo (p=0.4). The authors of this study concluded that octreotide does not significantly increase the rate of spontaneous fistula closure compared to placebo.

Bile Acid Sequestrants

Cholestyramine

The majority of bile acid reabsorption occurs in the terminal ileum with only a small proportion (3-5%) being excreted into the feces (30). Excess bile acids that enter the colon stimulate secretion and increase colonic motility leading to diarrhea. Bile acid malabsorption can be the result of terminal ileal resection. When less than 100 cm of terminal ileum is resected, there is interruption of the normal feedback resulting in increased bile acid synthesis and an increase in the concentration of unabsorbed bile acids entering the colon. However, when more than 100 cm of distal ileum is resected, the reduction in bile acid absorption exceeds the liver's ability to synthesize adequate replacement which ultimately results in a decreased bile acid pool and impaired fat digestion. Cholestyramine is a bile acid sequestrant that forms an insoluble complex that is excreted in the stool preventing secretory actions of bile acids within the colon (30). In patients without colon-in-continuity, the use of cholestyramine may further worsen fat malabsorption. Hofmann et al. conducted a single-blind "a-b-*a*" design trial to evaluate the use of cholestyramine in 12 patients with less than 100 cm of ileal resection and eight patients with greater than 100 cm of ileal resection (31). Each patient received a box containing 24 packets labeled "A," 24 packets labeled "B," and 24 packets labeled "C". Packets A and C contained 4g of placebo and packet B contained 4g cholestyramine. The patients were told that these packets contained different drugs that may or may not help their diarrhea and were instructed to take one packet before each meal and at bedtime and to record fecal frequency and consistency. Ten of 12 patients with less than 100 cm of ileal resection had a reduction in fecal frequency with use of cholestyramine, however none of the patients with greater than 100 cm of ileal resection responded. The authors concluded that cholestyramine is a useful symptomatic treatment for diarrhea in patients with small ileal resections and mild steatorrhea.

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