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Summary of the Causative and Treatment Factors of Diarrhea and the Use of a Diarrhea Assessment and Treatment Tool to Improve Patient Outcomes

ABSTRACT

This article is a review of the causative factors and pharmacologic treatments of diarrhea. This information was incorporated into a Diarrhea Assessment and Treatment Tool (DATT) to guide clinicians on comprehensive diarrhea assessment and current treatment recommendations. The tool was utilized at a university-affiliated oncology institution by a clinical nurse specialist on 26 patients as a performance improvement project. Ease of use and efficacy of DATT were tested. Eighty-one percent of patients were assessed using DATT in 30 minutes or less. Seventy-nine percent of the 57 identified diarrhea classifications were not being treated upon initial assessment. Diarrhea control was achieved in 73% of the patients within 7 days or fewer when DATT was utilized. The premise of diarrhea management is that if all the causative factors are not treated, diarrhea will persist. The conclusions are that this tool will aid the clinician in a comprehensive assessment of diarrhea and provide a systematic approach to diarrhea treatment. The need for research on best practice for management of the various causative factors of diarrhea is needed.

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A national survey of oncology nurses with experience in cancer-related diarrhea revealed that a significant number of patients are being treated for diarrhea due to cancer and its treatment (Rutledge & Engelking, 1998). In addition, clinicians at a large teaching cancer hospital observed an increasing number of patients being admitted to the hospital for diarrhea and its related symptom of dehydration.

Inadequate management of cancer-related diarrhea can be attributed to patient underreporting, inconsistent methods of assessment and treatment, and insufficient data with which to develop appropriate treatments (Rutledge, & Engelking, 1998). Currently, no standardized tool exists to assess and treat diarrhea. To improve the current practices used to provide adequate treatment for diarrhea, an interdisciplinary group was formed under the leadership of a clinical nurse specialist (CNS) in bowel and symptom management to develop such a tool.

Background Information on the Causes of Diarrhea

There are multiple types of diarrhea. This requires that individualized treatment of patients is paramount. The

first task of this interdisciplinary group was to identify the different types of diarrhea. Knowledge of the different types of diarrhea and the respective treatments enables practitioners to readily determine which types need to be treated. The premise is that if all causes of diarrhea are not addressed in the treatment plan, the condition will likely persist.

An interdisciplinary diarrhea study group was formed to devise a tool that would guide clinicians in assessing the cause(s) of, and developing a treatment plan for, diarrhea. This group comprised advanced practice nurses, clinical pharmacists, clinical dietitians, physician assistants, and a wound, ostomy, and continence nurse.

This study group used the classifications of diarrhea defined in the literature as a basis for formulating the Diarrhea Assessment and Treatment Tool (DATT). The six categories of diarrhea outlined were as follows: dysmotility, malabsorptive, osmotic, secretory, exudative, and chemotherapy-induced diarrhea (CID) (Hogan, 1998; Rutledge, & Engelking, 1998). On the basis of similar physiologic effects on the gastrointestinal (GI) mucosa, it was decided to combine the secretory, exudative, and CID categories into a single category. Because the management of these three types of diarrhea is similar (Viele, 2003), this combination category was named secretory/exudative. Benson et al. (2004) revised their guidelines for the treatment of cancer treatment-induced diarrhea to be inclusive of radiotherapy-induced diarrhea along with chemotherapy. Our definitions also reflect this inclusion.

Dysmotility Diarrhea

Dysmotility diarrhea can be caused by a surgical resection of any part of the GI tract, irritable bowel syndrome, anxiety, and any medications that speed up GI motility. Dysmotility diarrhea results in decreased transit time through the GI tract, which causes stool to move through the GI tract faster than normal. Decreased transit time does not allow adequate time for absorption of nutrients, electrolytes, and fluids to occur. Multiple factors have been identified as the cause of this type of diarrhea and are described in the following text.

Limited Exposure of the Luminal Contents to Mucosal Surface

Because GI contents move quickly through the GI tract, normal mucosal functions cannot occur following gastrectomy, ileocecal valve resection, and intestinal resection. Treatment is intended to slow GI motility by regulating the transit of fluids, fiber, food, and medications. Large meals normally cause a massive downward peristaltic push. Clinically, it has been observed that an increased amount of fluid with meals or drinking hot liquids at any time causes increased peristalsis and thus more stooling.

Dietary fiber can help speed up or slow down intestinal transit time (Godding, 1980). This finding was the basis of a 1992 Quality Improvement report at The University of Texas M. D. Anderson Cancer Center to decrease the frequency of stooling in patients following colorectal surgery. Eighty-six percent of patients who were compliant with the program had positive results, using 3.4 g of psyllium or 1 tsp of methylcellulose in 2 ounces of water after a meal, with no fluids for 1 hour afterward. The patients took their first dosage with breakfast and every 5 days, added a one-teaspoon dose to another meal and a one-teaspoon dose at bedtime until they reached a maintenance dose that resulted in a decreased number of stools per day (Bisanz, 2005). In addition, spicy, deep-fried foods and foods that are unique to an individual that increase peristalsis were eliminated from the patients' diets. Medications that speed GI motility (e.g., magnesium, sorbitol, and prokinetic drugs) were discontinued, and other drugs causing diarrhea were compensated for by diet and/or alternative pharmacotherapy. When caring for patients with enteral tubes, it is important to assess for any sorbitol content in liquid medications, which can increase GI motility.

Alterations in Mechanical Stretch Receptors or Neural Stimuli

According to Engelking (2004), peristaltic dysfunction can be in response to alterations in the variety of mechanical stretch or neural stimuli. An example of peristaltic dysfunction is fecal impaction caused by opioid therapy for pain. This condition can result in overflow diarrhea, causing liquid stool to seep around the impaction from the small bowel. The standard treatment is manual disimpaction, followed by milk and molasses enemas at a volume of less than 300 ml given high (12 in.) up to transverse colon. Insert enema tube with patient on left side. Turn patient to right side, release solution, and clamp enema tube. Do not remove for 20 minutes while patient stays on right side so the solution can be distributed into the transverse and ascending colon. An obstructive process that distends the bowel beyond its normal size is another example of how motility can be affected.

Peristaltic Stimulants

Stimulant laxatives (e.g., sennosides and bisacodyl) and prokinetic agents (e.g., metoclopramide and erythromycin) increase GI motility.

Disease States

Irritable bowel syndrome, spastic colon, and functional bowel syndrome are examples of diseases that can result in diarrhea.

Psychological Factors

Stress, anxiety, and fear can contribute to motility disorders secondary to psychoneuroimmunologic systems.

Treatment Options

There are currently two major classes of drug therapy used to treat motility dysfunction: intestinal transit inhibitors and intraluminal agents. The intestinal transit inhibitors are opioids and opioid derivatives, including medications such as morphine, codeine, loperamide, and diphenoxylate, and are used for their central and peripheral effects on the intestine. Although they were once thought to only slow intestinal motility, these medications have also been shown to decrease intestinal secretions and increase intestinal fluid absorption and intestinal blood flow (De Luca & Coupar, 1996). These characteristics make these drugs a valuable resource for the treatment of diarrhea-associated motility dysfunction syndromes following gastrectomy, ileocecal valve resection, major intestinal resections, enterocolic fistula, inflammatory bowel disease, and partial bowel obstructions. Intestinal transit inhibitors are also beneficial for the treatment of secretory diarrhea, which will be described later.

Diphenoxylate is formulated with atropine (Lomotil) in an effort to decrease the development of opioid dependence. Atropine produces anticholinergic side effects, making it undesirable for use in some patients. The standard dosing schedule for this agent is one to two tablets orally three or four times daily (Levy, 1991). Loperamide (Imodium) was created through the modification of diphenoxylate in an effort to separate the central and local effects of opioids. Loperamide does not cross the blood–brain barrier, thereby alleviating the side effects of sedation and opioid dependence. The recommended dosage for loperamide is 4 mg orally once and then 2 mg orally after each bowel movement (maximum of 16 mg/day) or 2-4 mg orally four times daily. For acute diarrhea, loperamide has been shown to be more effective than over-the-counter agents and diphenoxylate/atropine (Cornet, Aspeling, & Mallegol, 1977; DuPont, Ericsson, DuPont, Cruz, & Mathewson, 1990). Administer as described earlier under dysmotility diarrhea. Loperamide has also proven to be efficacious in the treatment of chronic diarrhea and diarrhea secondary to bowel resections (Herbst, Kamm, & Nicholls, 1998).

When patients fail treatment with loperamide and diphenoxylate/atropine, the addition of codeine or deodorized tincture of opium (DTO) can be very effective. Codeine is less commonly used because of its propensity to cause sedation and nausea. The recommended dosage of codeine is 15-30 mg orally three to four times daily (Levy, 1991). Deodorized tincture of opium is typically reserved as an opioid of last resort and can be dosed at 0.3-1 mL orally four times daily (maximum 6 mL/day). Because 0.3 mL of DTO is comparable with 3 mg of morphine, 1 mL of DTO orally four times daily is equivalent to a total of 40 mg of morphine daily (Cohen & Pops, 1968; Klasco, 2005). Combination opioid therapy may be necessary in more complex cases of dysmotility diarrhea. Use of any opioid or opioid derivative (excluding loperamide) will necessitate a taper upon discontinuation to prevent syndromes such as opioid withdrawal or rebound diarrhea.

Another group of compounds used to treat dysmotility syndromes are intraluminal agents. Examples include psyllium, methylcellulose, and cholestyramine. Psyllium and methylcellulose absorb extra fluid within the bowel to create more formed stools (DuPont, Flores, & Ericsson, 1990). Cholestyramine (Questran) is a bile acid sequestrant prescribed to patients with a history of ileum resection and intact colon. Bile is produced in the liver, secreted into the duodenum to help with fat emulsification in digestion, selectively reabsorbed in the ileum, and then recycled back to the liver via enterohepatic circulation. In patients who have had a significant ileum resection, bile acids are dumped into the colon, producing bile acid diarrhea. The dose of cholestyramine is 4 g orally twice a day (maximum 24 g/day) (Lord, Schaffner, DeCross, & Sax, 2000).

Malabsorptive Diarrhea

Malabsorptive diarrhea affects many types of patients, including those with celiac sprue, pancreatic exocrine insufficiency, and digestive enzyme insufficiency. Treatment of this type of diarrhea is directed at dietary modifications, enzyme replacement, or both.

Celiac Disease

Celiac disease (CD) is a genetic disorder characterized by permanent gluten intolerance, which leads to autoimmune enteropathy and intestinal malabsorption. *Gluten* is the term used for the compounds called prolamins, which are storage proteins found in the seeds of grains such as wheat, barley, and rye (Pietzak, Catassi, Drago, Fornaroli, & Fasano, 2001). These compounds are toxic to patients with this disorder, resulting in mucosal atrophy of the small intestine. Gastrointestinal symptoms, including diarrhea, bloating, steatorrhea, bulky and foaming stools with a foul odor, anorexia, and other weight loss conditions, typically occur. Extraintestinal symptoms, such as neurological disorders, anemia, blunted growth, osteoporosis, dental enamel defects, reproductive problems, and endocrine disorders, can also result (Dewer & Ciclitira, 2005; Pietzak et al., 2001).

Patients most commonly present with symptoms of CD in the first 2 years of life as gluten products are introduced into the diet. Recent reports suggest an increasing number of CD diagnoses occurring during adolescence and middle age, suggesting that healthcare professionals should not look at CD as just a childhood disease (Dewer & Ciclitira, 2005). If CD is suspected, tissue transglutaminase is the current standard for screening for CD due to its high specificity and sensitivity

(Freeman, 2008); however, the gold standard for diagnosis remains small-bowel biopsy. The primary treatment for CD is a gluten-free diet (GFD), which results in clinical recovery for the majority of the patients. Excluding all foods containing gluten (chiefly buckwheat, malt, oats, rye, barley, and wheat) is the basic principal of diet therapy for CD. For those refractory to GFD, further testing should be performed to rule out other infectious and noninfectious causes of enteropathy (Pietzak et al., 2001).

Pancreatic Insufficiency

Pancreatic insufficiency occurs when at least 90% of pancreatic exocrine secretion is lost. This loss can be caused by long-standing pancreatitis, pancreatic ductal obstruction, or pancreaticoduodenectomy (Whipple procedure). After the ingestion of a high-fat meal, patients with pancreatic insufficiency will experience abdominal bloating, gas, and steatorrhea. Pancreatic enzyme supplementation provides active enzymes to the duodenum for use in the hydrolysis of fat, proteins, and starch in the diet (Layer & Keller, 2003). The recommended oral dosage for enzyme replacement in adults and children is one to three capsules with each meal and one capsule with snacks. Dose titration may be necessary depending on patient reports of continued symptoms.

There is a lack of consistency in enzyme activity (i.e., actual vs. labeled enzyme activity) among the different enzyme preparations affecting the amount of active enzyme that reaches the small intestine. Changing from brand-name enzyme replacement products to generic ones or switching between generic products is not recommended (Hendeles, Dorf, Stecenko, & Weinberger, 1990). Concomitant use of histamine-2 (H_2) receptor antagonists (e.g., famotidine or ranitidine) or proton-pump inhibitors (e.g., omeprazole, lansoprazole, or pantoprazole) may increase the effect of pancreatic enzyme supplementation by allowing less degradation of the enzymes while in contact with gastric acid (Layer & Keller, 2003).

Lactose Intolerance

Lactose intolerance is a common digestive enzyme alteration that causes malabsorptive diarrhea. Lactose intolerance is divided into three distinct categories: primary, secondary, and total lactase deficiency (Swagerty, Walling, & Klein, 2002). Primary lactose intolerance develops over time, as lactase levels decrease shortly after weaning and remain depressed throughout life. People of Asian, African, and Native American ancestry have a higher incidence of depressed lactase levels than people of Northern European ancestry. Infections, GI illness, and diseases causing structural damage to the intestinal mucosa describe the etiology of secondary lactose intolerance. This type may be reversible with resolution of the causative insult. The third distinct category involves a total lactase deficiency and it is the least common of the three types.

Typical symptoms of lactose intolerance are GI in nature and include abdominal pain, distention, flatulence, nausea, and diarrhea after the ingestion of milk or of other dairy products. Reducing the intake of products containing milk or dairy products is the mainstay of treatment. It is important to realize that lactose intolerance is not synonymous with a milk allergy. If the diagnosis is milk allergy, the treatment is strict elimination of dairy proteins. The degree of dietary lactose reduction is patient specific, with the majority of patients able to tolerate small amounts of milk or dairy products throughout the course of a day.

Many hidden sources of lactose are present in processed foods, requiring lactose-sensitive patients to keep track of foods that exacerbate their condition (Matthews, Waud, Roberts, & Campbell, 2005). Products containing lactase, such as Dairy Ease® and Lactaid®, enable some individuals to ingest increased amounts of dairy products; however, these products should be used as a supplement to a lactose-restricted diet and not as a substitute. Patients who are lactose intolerant must make sure they get an adequate calcium intake (1,200-1,500 mg/day) to prevent long-term consequences of osteoporosis. This calcium level can be easily obtained with diet modifications and the use of supplements (Swagerty et al., 2002).

Osmotic Diarrhea

Osmotic diarrhea results from the ingestion of unusually high amounts of poorly absorbed and osmotically active solutes, such as mannitol, sorbitol, lactulose, and the magnesium salts contained in antacids and laxatives (Table 1) (Chassany, Michaux, & Bergmann, 2000; Ratnaike & Jones, 1998). These solutes draw in water across the GI mucosa.

Lactulose, a synthetic disaccharide that humans cannot absorb, was developed as a laxative on the basis of physiologic mechanisms of osmotic diarrhea. Reaching the colon unchanged, lactulose is metabolized by enteric bacteria into lactic, acetic, and formic acids. These acids osmotically pull water into the colon, which leads to diarrhea (Sellin, 2001). Osmotic diarrhea may also occur in response to magnesium salts and is dose dependent.

Ampicillin is associated with a 5% incidence of diarrhea, which because of the alteration of the normal intestinal flora causes abnormal carbohydrate absorption (Tedesco, 1975). Acarbose, a medication used in diabetes management, can lead to osmotic diarrhea by inhibiting the intestinal enzyme glucosidase, which breaks down carbohydrates into monosaccharides in the GI tract. The accumulated carbohydrates ferment,

TABLE 1. Principal Drugs Implicated in Osmotic Diarrhea

Cathartic laxatives Lactulose, sorbitol, fructose, and mannitol
Magnesium Laxatives, antacids, and sugar substitutes
Secondary to maldigestion of carbohydrates Anti-infectives (ampicillin) Acarbose (α-glucosidase inhibitor)

causing flatulence and diarrhea. Treatment of osmotic diarrhea usually involves elimination of the offending agent, followed shortly by resolution of symptoms.

Secretory and Exudative Diarrhea

Secretory Diarrhea

Secretory diarrhea occurs when there is a net secretion of fluid and electrolytes into the lumen. Normally, water moves from the lumen of the GI tract into the tissues, and this movement is controlled by the transport of charged ions. When ion transport is disrupted, the net flow of water out of the tissues and into the lumen can result in diarrhea. Secretory diarrhea is characterized by large stool volumes; absence of red or white blood cells in the stool, fever, or systemic symptoms; persistence of diarrhea with fasting; and lack of a stool osmotic gap (Field, 2003; Fine & Schiller, 1999).

A classic example of acute secretory diarrhea is cholera. *Vibrio cholerae* produces cholera toxins that cause uncontrolled secretion of water. Similar symptoms are seen in patients with enterotoxigenic *Escherichia coli* infection (Baldi, Bianco, Nardone, Pilotto, & Zamparo, 2009). Chronic secretory diarrhea is commonly attributed to various hormones. Carcinoid tumors secrete serotonin, bradykinin, substance P, and prostaglandins, all of which are secretory stimuli in the intestine. In patients with VIPoma, also known as pancreatic cholera, large quantities of vasoactive intestinal polypeptide (VIP) hormones are secreted that stimulate intestinal secretion. In patients with medullary carcinoma of the thyroid, another secretory stimulus, calcitonin, is released (Field, 2003).

Antibiotic-Associated Diarrhea

Antibiotic-associated diarrhea (AAD) is defined as unexplained diarrhea that is temporarily associated with the use of antibiotics (Bartlett, 2002). It occurs in up to 29% of patients with diarrhea, with up to 25% of those cases attributed to *Clostridium difficile* (Katz, 2006). Alteration of the normal gut flora allowing the overgrowth and colonization of pathogenic bacteria is the most frequent mechanism cited as causing AAD. Other mechanisms, however, have been suggested. One includes the reduction in fecal anaerobe concentration due to antibiotic use can lead to abnormal carbohydrate metabolism and decreased bile acid breakdown.

Another mechanism involves the direct toxic effects of broad-spectrum antibiotics that are seen with erythromycin and other macrolide antibiotics. These agents stimulate motilin receptors in the GI tract producing peristalsis and increased motility (Bartlett, 2002). Risk factors identified for the development of AAD include the extremes of age (<6 years or >65 years), length of hospitalization, nasogastric tube use, chronic or severe illness, immunosuppression, chemotherapy treatment, GI surgery, prolonged or repeated use of antibiotics, use of broad-spectrum antibiotics, and antibiotics with high biliary excretion (Kale-Pradham, Jassal, & Wilhelm, 2010).

Antibiotic-associated diarrhea can present as diarrhea without complications or as colitis producing symptoms such as fever, abdominal pain, hypoalbuminemia, and leukocytosis (Bartlett, 2002). Subsequent complications seen with colitis can include hypokalemia, dehydration, acute renal failure, perforation of the colon, shock, and rare cases of toxic megacolon.

Clostridium difficile-Associated Diarrhea

Clostridium difficile is a gram-positive, spore-forming, anaerobic bacillus that produces bacterial toxins. Ninety percent of *Clostridium difficile*–associated diarrhea (CDAD) infection is associated with antibiotic use because of a disruption of normal gut flora. *Clostridium difficile* produces pseudomembranous lesions in the colonic mucosa, leading to a severe inflammatory response and destruction of the mucosal lining. The symptoms and complications of CDAD infection are similar to colitis-associated AAD and can be life threatening in severe cases.

It is important to note that the onset of both AAD and CDAD usually occurs within 4-9 days after stopping the offending antibiotic but can emerge as late as 8 weeks (Rohde, Bartolini, & Jones, 2009). *Clostridium difficile* spores can remain in the gut hidden within the colonic diverticula, even after aggressive treatment. This allows the microorganism to avoid peristalsis and exposure to medication treatment, resulting in treatment failures and high recurrence rates (Tedesco, Gordon, & Fortson, 1985). The recurrence of CDAD can be up to 24% within 2 months and even higher in those with two or more previous episodes (Rohde et al., 2009; Sunenshine & McDonald, 2006). Diagnosis of CDAD is through positive stool toxin assay along with clinical symptoms of infection.

Exudative Diarrhea

Exudative diarrhea results from direct damage to the small or large intestinal mucosa. An inflammatory or ulcerative process in the GI tract results in exudative diarrhea when there is a release of excessive mucous, serum

protein, blood, and fluids into the bowel (Engelking, 2004; Engelking, Rutledge, Ippoliti, Neumann, & Hogan, 1998; Rutledge & Engelking, 1998). The barrier function of intestinal epithelium is compromised by loss of both epithelial cells and hydrostatic pressure in blood and lymphatic vessels, causing water, electrolytes, mucus, and protein to accumulate within the lumen.

Examples of exudative diarrhea include inflammatory disorders of the gut, such as Crohn disease and ulcerative colitis, infections caused by *Salmonella* and *Shigella,* chemotherapy-induced diarrhea (CID), and radiation-induced enteritis (Thompson, 2000; Shah, 2004). The cells of the intestinal villi are particularly affected when radiation treatment fields include the GI tract because of the rapid rate of cell proliferation. The villi become flat or disappear and ulcers can appear and decrease the absorptive ability of the GI tract. When the nutrients and water cannot be adequately digested or absorbed, diarrhea will occur and malnutrition and electrolyte imbalance can result.

Radiation-induced diarrhea usually occurs 1-2 weeks after the start of radiation therapy and continues for 1-2 weeks after the completion of treatment. The incidence and severity of radiation-induced diarrhea is directly related to the dose of radiation. Late and chronic radiation enteritis is secondary to mucosal atrophy and fibrosis (Rutledge & Engelking, 1998).

Another example of exudative diarrhea is CID. Chemotherapy generally works by destroying rapidly dividing cancer cells while damaging normal rapidly dividing cells, such as the epithelial lining of the GI tract. Damage to the cells lining the GI tract can lead to a disruption in the delicate fluid balance that they normally maintain. Reabsorption of fluid from the GI tract back into the body is decreased, and secretion of fluid and electrolytes in the stool is increased. This disruption leads to watery bowel movements known as CID (Sharma, Tobin, & Clarke, 2005). If not adequately managed, CID can lead to dehydration, serum electrolyte imbalances, acute renal insufficiency, impaired immune function, malnutrition, inflammation, pain, and bleeding. These conditions can be life threatening.

The severity of diarrhea as rated by the National Cancer Institute Common Toxicity Criteria is based on the number of bowel movements per day above baseline (Table 2). It may be helpful, however, to measure stool volume in order to assess treatment needs because recording the number of stools does not provide information on the quantity. The amount of fluid loss provides information that guides a medication regimen to prevent dehydration. Patients should be instructed on how to maintain this record at home. These considerations were incorporated into the DATT (Appendix A).

Some chemotherapy and biological agents used to treat cancer are more prone to cause diarrhea than do others. Table 3 identifies some of the most common chemotherapy and biological drugs that can cause diarrhea and the incidences of diarrhea associated with them. Other factors, such as GI surgery, radiation therapy, diabetes mellitus, irritable bowel syndrome, and pancreatic insufficiency, can exacerbate CID. Antimicrobial agents, metoclopramide, and oral magnesium can also aggravate CID (Arnold et al., 2005). It is important for practitioners to identify potential risk factors that could amplify CID to reduce its severity. It is also essential to educate patients and family members about the potential for CID and its appropriate management based on their chemotherapy treatment. Patients should always be instructed to contact their physician if they are unable to manage their diarrhea to prevent potentially life-threatening complications.

Treatments

Dietary restrictions help palliate the symptoms of radiation-induced diarrhea. Patients are put on a low-residue diet (no greasy foods, raw vegetables, chocolate, caffeine, or alcohol) and are encouraged to drink 3 L of fluid per day; eat small, frequent meals; and avoid hot liquids and dairy products. Limiting fluid with meals to 8 oz can also be beneficial. Encourage patients to include foods high in potassium ions in their diets. Nutmeg has also been shown to decrease GI motility (Yasko, 1982). In addition to dietary alterations with secretory and exudative diarrhea, it is helpful to give intestinal transit inhibitors as used in motility dysfunction. Start with up to 8 loperamide tablets per day; if that is not successful, alternate 1 diphenoxylate/atropine tablet with 2 loperamide tablets every 3 hours. If that approach is not effective, increase to 2 diphenoxyhlate/atropine tablets alternated with 2 loperamide tablets every 3 hours. If patient does not have a stool since last dose, hold next dose until stooling begins again. When this regimen fails, an opioid can be prescribed.

TABLE 2. National Cancer Institute Common Toxicity Criteria

Grade 1	Increase of less than four stools per day over baseline
Grade 2	Increase of four to six stools over baseline
Grade 3	Increase of greater that seven stools per day over baseline incontinence
Grade 4	Life-threatening consequences including extremely low blood pressure as a result of severe dehydration
Grade 5	Death

The exception to using intestinal transit inhibitors in secretory diarrhea is diarrhea caused by enterotoxin-producing bacteria, in which the use of such agents is contraindicated (G. D. Searle LLC, 2005). Antimicrobial agents are indicated for these cases.

For patients with refractory secretory diarrhea, octreotide, an analog of somatostatin, may prove beneficial. Octreotide inhibits gastrin, serotonin, VIP, and other hormones, resulting in reduced splanchnic blood flow. Octreotide is indicated for treating severe, watery diarrhea resulting from carcinoid tumors and VIP-secreting tumors (Novartis Pharma Stein AG, 2010). Octreotide can be initiated at 100 to 200 mcg subcutaneously every 8 hours and increased in 50-mcg increments up to 500 mcg subcutaneously every 8 hours. In severe cases, dose escalations of 100 mcg may be necessary, with a maximum dose not to exceed 500 mcg subcutaneously every 8 hours (Harris et al., 1995). Once acute diarrhea is resolved, octreotide should be adjusted to maintenance doses to achieve therapeutic benefit at the lowest dose necessary.

Alternatively, the long-acting depot formulation may be administered monthly once therapeutic efficacy is achieved with immediate-acting octreotide. It is recommended that an overlap of 2 weeks occur when switching patients from immediate-release octreotide to the long-acting depot formulation. Dosages range from 10 to 30 mg intramuscularly every 4 weeks (Novartis Pharma Stein AG, 2010b). In cases of severe life-threatening diarrhea, octreotide may be administered via continuous intravenous infusion.

TABLE 3. Agents Commonly Causing Diarrhea (Hoff et al., 2001; Klasco, 2005)

Agent	Grade	Incidence
Oxaliplatin (Eloxatin)	3/4	4% (oxaliplatin alone), 11% (with 5-fluorouracil plus leucovorin)
Docetaxel (Taxotere)	2/3	39% (doses of 100 mg/m^2), 23% (doses of 75 mg/m^2)
Paclitaxel (Taxol)	1/2	38%
Topotecan (Hycamtin)	1/2	42%
Irinotecan (Camptosar)	3/4	8% (early onset), 30% (late onset)
5-Fluorouracil	3/4	15% (bolus), 25%-30% (continuous infusion)
Capecitabine (Xeloda)	3/4	15%
Gefitinib (Iressa)	1/2	49% (doses of 250 mg), 76% (doses of 500 mg)
Cetuximab (Erbitux)	3/4	22%

The antisecretory effects of anti-inflammatory agents such as sulfasalazine, aspirin, and ibuprofen make them attractive in the management of exudative diarrhea. These agents block cyclooxygenase, inhibiting prostaglandin production in the bowel mucosa. Corticosteroids also have anti-inflammatory properties and can be used for severe cases of secretory diarrhea (Cavagnaro, Berezin, & Medow, 2003).

Several adsorbents can be used to control diarrhea, especially that is associated with refractory radiation-induced colitis. The goal of these agents is to increase stool consistency, thereby decreasing the amount of liquid stool excreted. Examples of adsorbents include activated charcoal, bismuth, sucralfate, and cholestyramine. One disadvantage of intestinal adsorbents is their interference with the absorption of numerous medications; nutrients and digestive enzymes; as well as toxins, bacteria, and other noxious materials in the GI tract. A careful inspection of a patient's medication history should be done to prevent these drug interactions.

In addition to treating diarrhea, activated charcoal can be helpful in reducing odor associated with ostomy output (Klasco, 2005). Bismuth subsalicylate is used in treating dyspepsia and infectious diarrhea and in combination with other antimicrobials for treating peptic ulcer. Bismuth provides antimicrobial activity against *E. coli* and *V. cholerae* enterotoxins often present in traveler's diarrhea (DuPont et al., 1987; Lambert, 1991), and salicylate possesses antisecretory properties. The typical dosage is two tablets (525 mg) orally four times daily. Salicylates should not be prescribed to patients with aspirin allergies, viral illnesses, or immunosuppression; children younger than 3 years; and women in their third trimester of pregnancy (Klasco, 2005).

Controversy exists regarding the efficacy of sucralfate in the prevention and treatment of radiation-induced colitis. Sucralfate is a nonabsorbable, aluminum-based compound that forms a protective GI barrier when it comes into contact with the GI mucosa; however, the mixed results of numerous clinical trials and the potential of GI symptom exacerbation (e.g., indigestion, nausea, and vomiting) do not provide strong evidence for its use in treating diarrhea (Benson et al., 2004). The typical dosage of sucralfate is 1-2 g orally two to four times daily.

Antimicrobial agents can be very effective in treating infectious diarrhea, particularly because of enterotoxins produced by *C. difficile*. Metronidazole, which covers most gram-positive

and gram-negative anaerobes, is the drug of choice for treating CDAD. The usual dosage is 500 mg orally three times daily or 250 mg orally four times daily. In patients who do not respond to metronidazole, oral vancomycin can be given, which acts locally to treat pseudomembranous enterocolitis with minimal absorption. The usual dosage is 125-250 mg orally four times daily. If patients are unable to take oral antibiotics, intravenous metronidazole at the earlier mentioned dosages can be used. This is the only option available, as it provides moderate concentrations of the drug in the colon (Fekety & Shah, 1993).

The duration of therapy for metronidazole and vancomycin is typically 10-14 days. When a patient is being treated for CDAD, it is important to discontinue the offending antibiotic, if possible. It is also prudent to avoid the use of antiperistaltic agents (i.e., loperamide and opiates), as these agents promote retention of the toxin and increase the possibility of developing toxic megacolon.

Probiotics have shown promise in the prevention and treatment of AAD (including CDAD infection). Probiotics are defined as "live microorganisms, which when given in adequate amounts, confer a health benefit on the host" (Hoffman, Heimbach, Sanders, & Hibberd, 2008). They are used to restore intestinal microbial balance, thus inhibiting pathogens and toxin-producing bacteria. *Saccharomyces boulardii* and *Lactobacillus rhamnosus GG* are two probiotics that have been studied in AAD and CDAD.

Saccharomyces boulardii is a nonpathogenic yeast, with reasonable evidence supporting its use in adults for primary prevention of AAD and prevention of recurrent CDAD infections. Currently, there is not enough evidence to support its use in children (Katz, 2006; Rohde et al., 2009). Dosing for *S. boulardii* is 1 g oral daily.

Lactobacillus rhamnosus GG is an acid- and bile-stable strain of *L. rhamnosus* isolated in 1983 from the intestinal tract of a healthy human being. It reduces the risk of AAD in children and has been found in case reports and small case series to be effective in the primary prevention or the prevention of CDAD recurrent infections (Katz, 2006; Rohde et al., 2009). Dosing of *L. rhamnosus GG* in children is recommended at (1-2) $\times$ 10^{10} CFU daily.

The role of probiotics in AAD and CDAD warrant further study and formal cost-benefit analysis. Because of reports of fungemia and bacteremia during treatment with commercially available probiotics, their use in the immunocompromised patient should be avoided (Katz, 2006).

Nutritional Management of Acute Cancer Treatment–Induced Diarrhea

Initial management of mild to moderate diarrhea should include dietary modifications (e.g., eliminating all lactose-containing products and high-osmolar dietary supplements). Although complete resolution of diarrhea may not be possible for some patients, it can be minimized with appropriate dietary modifications or bowel rest, depending on the clinical situation (Hogan, 1998). Patients with severe or prolonged diarrhea may require total parenteral nutrition until the underlying cause is identified and controlled. Patients should be advised to eat small, frequent, bland meals and to adhere to a low-residue diet (Table 4).

Because of the multiple factors associated with diarrhea development, it is important for the clinician to identify all causative factors so that comprehensive treatment is accomplished. Unless this process is undertaken, diarrhea will continue to persist. The types of diarrhea, their characteristics, and examples are summarized in Table 5.

Methods

Application of the DATT

A thorough medical history and physical examination of each patient are crucial in determining the appropriate management of diarrhea. This includes the cancer diagnosis; prior chemotherapy, surgery, and radiation treatments; and medication history. Information regarding the amount and characteristics of the stool should be obtained to determine the severity of diarrhea. Other

TABLE 4. Foods to Avoid When on a Low-Residue Diet

Alcohol
Caffeine
Chocolate
Dairy products containing lactose
Dietary fiber Brown rice Fruits (including skin) Popcorn Vegetables (including skin) Whole-grain cereals, bread, and pasta
Gas-producing foods
Greasy foods
High-osmolar dietary supplements
Sorbitol-containing fruit juices
Spicy foods
Sugar alcohols Maltitol Mannitol Sorbitol Xylitol

TABLE 5. Diarrhea Classifications, Characteristics, and Examples

Diarrhea Class/Characteristics	Examples
Dysmotility diarrhea	
• Dysfunctional intestinal motility	• Colorectal resection
• Rapid transit and decreased exposure of luminal contents to the intestinal wall	• Drugs affecting peristalsis (i.e., metoclopramide, erythromycin)
	• Ileocecal valve resection
	• Irritable bowel disease, spastic colon, functional bowel syndrome
	• Irritable bowel disease
	• Meals high in fluid intake, hot liquids, and spicy or deep-fried foods
	• Narcotic withdrawal
	• Postgastrectomy
	• Stress, fear, and anxiety
Malabsorptive diarrhea	
• Gluten intolerance	• Celiac sprue
• Lack of pancreatic enzymes	• Pancreatic insufficiency
• Malabsorption of solutes	• Lactose intolerance
Osmotic diarrhea	
• Ingestion of an oral solute not fully absorbed	• Ingestion of nonabsorbable or hyperosmolar substances
• Rapid transit and decreased exposure of luminal contents to the intestinal wall	• Medications (i.e., acarbose, lactulose)
	• Enteral feeding
• Stool volumes are <l L/day	
• Stools decrease if patient is fasting	
• Na and K in feces is not altered	
Secretory/exudative diarrhea	
• Increased secretion of fluids and electrolytes	• Neuroendocrine tumors
• Interferes with digestive enzymes	• VIPoma
• Damage of intestinal mucosa decreasing the amount of functional mucosae and release of prostaglandins	• Gastrinoma
• Increased intestinal motility	• Carcinoid syndrome
• Persists when fasting	• Secretory adenoma
• Produces large volumes of stool >1 L/day	• Chemotherapy-induced diarrhea
	• Radiation colitis
	• Infections (i.e., *Clostridium difficile*-associated diarrhea, *Vibrio cholerae* infection, enterotoxigenic *Escherichia coli* infection)
	• Antibiotic-associated diarrhea
	• Inflammatory bowel disease (i.e., Crohn disease, ulcerative colitis)
	• Colonic malignancies

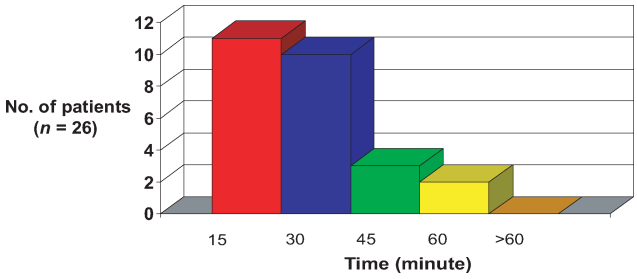

FIGURE 1. Time to complete assessment.

important components of patient assessment include a dietary history reflecting the types and amounts of food and fluids consumed daily, a report of previous antidiarrheal therapies used, and results of any pertinent laboratory or radiology tests. These recommendations were incorporated into the DATT.

After a review of the causes of diarrhea and the different therapeutic options for each of the classifications of diarrhea, the DATT was formulated. This tool includes clinical assessment, classification of the types of diarrhea, and appropriate treatment components (Appendix). This comprehensive tool provides clinicians with a single resource for use in determining the potential causes of diarrhea. We purposefully excluded graft versus host disease in the utilization of this tool. Because of its complex nature, it is managed by the primary transplant team.

Twenty-six adult patients were assessed using the DATT. These patients were identified for the use of the DATT through referral to a CNS or clinical pharmacy specialist for diarrhea management. Upon consult, the CNS evaluated the patients by using DATT for assessment and treatment of diarrhea.

Results

In all 26 cases, the DATT was useful in organizing the practitioner's thinking regarding the etiology of diarrhea. Each DATT was completed in less than 60 minutes; 81% (21/26) were completed in 30 minutes or less (Figure 1). Regarding the classifications of diarrhea by using the DATT, 4 patients had one diarrhea classification, 14 patients had two classifications, 7 patients had

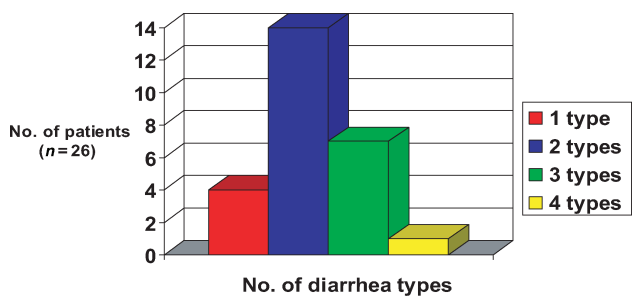

FIGURE 2. Number of diarrhea types identified (n = 57).

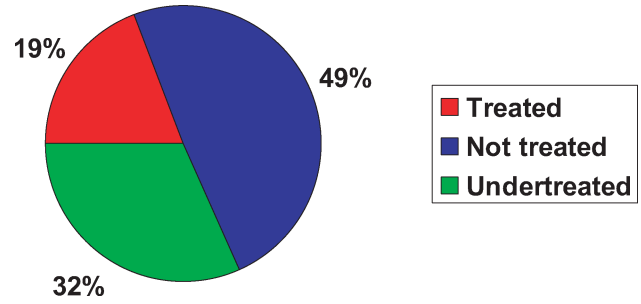

FIGURE 3. Assessment findings (n = 57).

three classifications, and 1 patient had all four diarrhea classifications (Figure 2). We also noted that 46 (81%) of the 57 identified diarrhea classifications were not being treated or were being undertreated (Figure 3). In one case, the patient refused treatment. Diarrhea control was achieved within 7 days, using the DATT in 19 patients (73%) (Figure 4). Of the remaining seven patients, one was lost to follow-up, two did not adhere to the treatment regimen, two required between 8 and 9 days to achieve diarrhea control, one was discharged to hospice care, and one required 3 months to achieve diarrhea control. Multidisciplinary involvement was not required for the majority of patients. Only 10 patients (38%) needed the additional involvement of the dietitian, nurse, pharmacist, or primary oncology team for control of the patient's diarrhea.

Discussion

In our study, the DATT was shown to be (1) useful for organizing the practitioner's thought process, (2) easy to use, and (3) valuable in providing symptom palliation within 7 days for approximately 75% of patients. Our study did have some limitations. There were a small number of patients who were evaluated by one CNS; use of the DATT by other medical practitioners has not been assessed. The DATT has not been validated and has been used only in an oncology population. Its applicability to patients with other diseases has not been determined.

We recommend that the DATT be used to evaluate patients with diarrhea. Further research should include

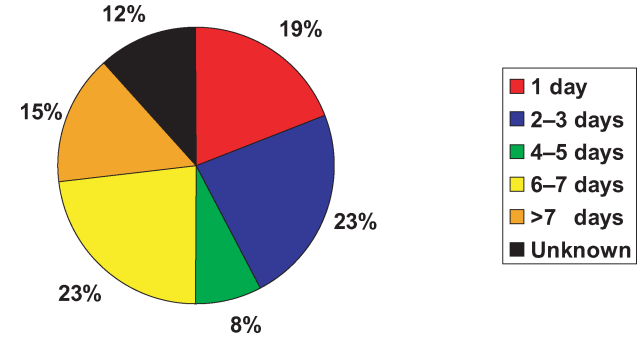

FIGURE 4. Time to diarrhea control (n = 26 patients).

a larger sample size and evaluation of future patients by all members of a multidisciplinary team. DATT validation needs to be pursued, and collaborative studies using the DATT in patients with and without cancer are encouraged. The DATT will be used for further studies to evaluate the causes of diarrhea, establish a diagnosis for diarrhea, and manage its treatment.

Conclusions

A review of the literature revealed the lack of an effective tool for evaluating and treating patients with diarrhea. The DATT addresses this lack of information needed to guide nurses and other healthcare practitioners in the comprehensive assessment and management of diarrhea. The use of DATT in this study suggests that the tool is beneficial, providing successful outcomes for 75% of the patients for whom the tool was utilized. On the basis of these initial findings, the multidisciplinary team should further research "best treatments" for the four categories of diarrhea addressed with this tool, which can lead to evidence-based guidelines for the treatment of diarrhea. ✪

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APPENDIX. Diarrhea Assessment and Treatment Tool (*Continues*)

MR#_____
Admission Date_____
Assessment Date_____

Patient History

Date diarrhea began _____

Cancer Diagnosis _____ Current Tx: Chemo _____ Abd XRT _____ Abd Surg _____

Diet History (check all that apply)
- ❑ Spicy foods
- ❑ High fiber foods
- ❑ Fried foods
- ❑ Fruit juices
- ❑ Hot liquids
- ❑ Caffeine products
- ❑ Dairy products
- ❑ Alcohol use: drinks/day _____

Fluid Intake (IV and/or po) for last 24 hours: 2000 mL (2 quarts) / day = Eight 8 oz glasses (240 ml per glass) of fluid / day
- ❑ <2000 mL/day (2 quarts)
- ❑ 2000 mL/day (2 quarts)
- ❑ >2000 mL/day (2 quarts)

Output _____

Volume of diarrhea per day
- ❑ < 500 mL
- ❑ 500–1,000 mL
- ❑ 1,001–1,500 mL
- ❑ >1,500 mL

Stool consistency
- ❑ Large
- ❑ Small
- ❑ Formed
- ❑ Semi-formed
- ❑ Liquid
- ❑ Watery
- ❑ Foul-smelling / floating
- ❑ Mucus
- ❑ Pus
- ❑ Bloody

Laboratory test results
- ❑ Stool for *C. difficile* toxin
- ❑ Stool for ova / parasites
- ❑ X-ray / CT scans
- ❑ Endoscopy
- ❑ Fecal fat
- ❑ 24-hour urine for 5-HIAA

Previous antidiarrheals used (Place dates patient started on medication in blank and dose to the side)
- _____Loperamide
- _____Diphenoxylate with atropine
- _____Deodorized tincture of opium
- _____Codeine
- _____Octreotide acetate
- _____Metronidazole
- _____Vancomycin
- _____ Antiinflammatory agents (dexamethasone, sulfasalazine)
- _____Medicinal fiber therapy (psyllium, methylcellulose)
- _____Herbal agents / alternative medications
- _____Lactobacillus
- _____Other

Diarrhea classifications (check all that apply)

Motility dysfunction
- ❑ Colorectal resection
- ❑ Gastrectomy
- ❑ Ileocecal valve resection
- ❑ Ileostomy
- ❑ Short bowel syndrome
- ❑ Irritable bowel syndrome, spastic colon, functional bowel syndrome
- ❑ Anxiety
- ❑ Medications affecting peristalsis (check circle)
  - ☐ Narcotic withdrawal
  - ☐ Metoclopramide
  - ☐ Erythromycin
  - ☐ Magnesium-containing drugs
  - ☐ Stool softeners
  - ☐ Laxative use / overuse

Malabsorption
- ❑ Lactose intolerance
- ❑ Pancreatic insufficiency
- ❑ Celiac Sprue

Osmotic
- ❑ Enteral nutrition
  - Date started_____
  - Type of tube feed and rate of enteral nutrition _____
  - Type of tube: ___JT, ___PEG ___DHT
  - Type of delivery: ___gravity bolus ___intermittent via pump
- ❑ Any oral liquid preparation containing sorbitol — cross reference with Micromedex (i.e, liquid KCl, liquid metoprolol)
- ❑ Sugar-free products

Secretory and Exudative
- ❑ Neuroendocrine tumors (VIPomas)
- ❑ Secretory adenoma
- ❑ Intestinal inflammation / infection – (*C. difficile*–associated diarrhea)
- ❑ Chemotherapy-induced diarrhea
- ❑ Neutropenic enterocolitis / typhlitis
  - Oral: _____
  - IV: _____
- ❑ Broad-spectrum antibiotics use (antibiotic-associated diarrhea)
- ❑ Inflammatory bowel syndrome (Crohn disease, ulcerative colitis)
- ❑ Radiation colitis

APPENDIX. (*Continued*) Diarrhea Assessment and Treatment Tool

Treatment Guidelines Based on Type of Diarrhea

	Recommended starting doses (write in effective dose to the side of agent)
❑ **Motility dysfunction**	
Intestinal transit inhibitors	
○ Diphenoxylate/atropine	1–2 tabs po tid-qid
○ Loperamide	4 mg x 1 then 2 mg after every BM (max 16 mg/d) **OR** 2–4 mg po qid
○ Deodorized tincture of opium (DTO)	0.3–1 mL po qid (max 6 mL/day)
○ Codeine	15–30 mg po qid (max 120 mg/day)
Intraluminal agent	
○ Psyllium, methylcellulose	Start with 1 tsp in 2 oz water after breakfast with **NO** fluid for 1 hr after. Increase per bowel Mgmt for Frequent stooling protocol
○ Cholestyramine (bile acid binder)	4 gm po bid (max 24 gm/day)
❑ **Malabsorption**	
Enzyme replacement	
○ Pancreatic enzymes	1–3 caps with meals and snacks increase prn
○ Lactaid (for lactose intolerance)	2–4 caps po tid-qid (with dairy products)
Diet modification	
○ Gluten-free diet (in diagnosed celiac disease)	Avoidance of wheat / gluten products in diet
❑ **Osmotic**	
○ Remove offending agent	
○ ____changed tube feeding formula from _____ to_____	
○ ____changed rate of formula administration from _____ to _____	
❑ **Secretory and Exudative**	
Antisecretory agents	
○ Diphenoxylate/atropine	1–2 tabs po tid-qid
○ Loperamide	4 mg x 1 then 2 mg after every BM (max 16 mg/d) **OR** 2–4 mg po qid
○ Octreotide	50–100 mcg Sq q8h (increase dose every 48h)
○ Antiinflammatory agents	
○ Sulfasalazine	500 mg po tid-qid
○ Dexamethasone	4 mg IV bid-tid
○ Enteric coated aspirin	325–mg po daily
○ Ibuprofen	200–400 mg po qid
Intraluminal agents	
○ Psyllium, methylcellulose	Start with 1 tsp in 2 oz water after breakfast with **NO** fluid for 1 hr after. Increase per bowel Mgmt for frequent stooling protocol
○ Bismuth	525–mg (2 tabs) po q1h prn (max 8 doses/day)
○ Activated charcoal	520–975 mg po after meals (max 4.16 g/day)
○ Sucralfate	1 gm po qid
Antimicrobials	
○ Metronidazole	250–500 mg po tid-qid x 10–14 days
○ Vancomycin	250–500 mg po qid x 10–14 days
Probiotic	
○ *Lactobacillus rhamnosus GG (LGG)*—children	1-2 x 10^{10} CFU po daily
○ *Saccharomyces boulardii (S. boulardii)*—adults	1 g po daily