

## Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea

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Submitted April 18, 2003; accepted March 2, 2004.

The closed roundtable meeting and development of this manuscript were supported by an unrestricted educational grant from Novartis Oncology, a division of Novartis Pharmaceuticals Corporation, East Hanover, NJ. Conflict of interest statements were signed by all participants, and Novartis Oncology was not involved in any of the discussions.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/04/2214-2918/\$20.00

DOI: 10.1200/JCO.2004.04.132

### ABSTRACT

#### Purpose

To update and expand on previously published clinical practice guidelines for the treatment of cancer treatment-induced diarrhea.

#### Methods

An expert multidisciplinary panel was convened to review the recent literature and discuss recommendations for updating the practice guidelines previously published by this group in the *Journal of Clinical Oncology* in 1998. MEDLINE searches were performed and the relevant literature published since 1998 was reviewed by all panel members. The treatment recommendations and algorithm were revised by panel consensus.

#### Results

A recent review of early toxic deaths occurring in two National Cancer Institute-sponsored cooperative group trials of irinotecan plus high-dose fluorouracil and leucovorin for advanced colorectal cancer has led to the recognition of a life-threatening gastrointestinal syndrome and highlighted the need for vigilant monitoring and aggressive therapy for this serious complication. Loperamide remains the standard therapy for uncomplicated cases. However, the revised guidelines reflect the need for recognition of the early warning signs of complicated cases of diarrhea and the need for early and aggressive management, including the addition of antibiotics. Management of radiation-induced diarrhea is similar but may not require hospitalization, and chronic low- to intermediate-grade symptoms can be managed with continued loperamide.

#### Conclusion

With vigilant monitoring and aggressive therapy for cancer treatment-induced diarrhea, particularly in patients with early warning signs of severe complications, morbidity and mortality may be reduced.

*J Clin Oncol* 22:2918-2926. © 2004 by American Society of Clinical Oncology

### INTRODUCTION

Diarrhea is a well-recognized side effect associated with a variety of chemotherapy agents, particularly fluorouracil (FU) and irinotecan (CPT-11), and with abdominal or pelvic radiotherapy (RT). The incidence of chemotherapy-induced diarrhea associated with modulated FU regimens, single-agent CPT-11, and the combination of FU plus CPT-11 has been reported to be as high as 50% to 80% of treated patients, and  $\geq 30\%$  of patients may experience grade 3 to 5 diarrhea.<sup>1-5</sup> The use of high-dose regimens (eg, bolus FU plus high-dose leucovorin)

and combination regimens (eg, CPT-11 plus bolus FU/leucovorin) is associated with a higher incidence of chemotherapy-induced diarrhea.<sup>2,6,7</sup> In particular, the CPT-11 plus bolus FU/leucovorin (IFL) regimen, administered as described by Saltz et al,<sup>8</sup> appears to be associated with an increased risk of treatment-related mortality compared with other commonly used regimens for the treatment of colorectal cancer.<sup>7</sup> This conclusion is based on two cooperative group trials in which at least some early deaths appear to have been related to gastrointestinal (GI) toxicity among patients receiving IFL. The fact that the IFL regimen had

become a standard first-line therapy for metastatic colorectal cancer in the United States highlighted the need to address this clinically important issue.

Although it has long been realized that diarrhea can be a serious, debilitating, and even life-threatening complication of cancer treatment, including chemotherapy and pelvic RT, until recently, little attention has been paid to the prospective evaluation and management of cancer treatment-induced diarrhea (CTID). Recent appreciation of the morbidity and mortality associated with chemotherapy-induced diarrhea in patients receiving IFL has again brought this issue to the forefront and heightened awareness of the need for standardized and universally accepted guidelines for the comprehensive evaluation and management of CTID. Loss of fluids and electrolytes associated with persistent or severe diarrhea can result in life-threatening dehydration, renal insufficiency, and electrolyte imbalances, and may contribute to cardiovascular morbidity. The risk of infectious complications is increased, which can lead to sepsis in patients with chemotherapy-induced neutropenia. In addition, CTID can have a serious impact on patient quality of life. Furthermore, it is important to consider that CTID can lead to changes in treatment, including dose reduction or discontinuation of therapy, that may have a negative effect on clinical outcome.<sup>9</sup> Therefore, the oncology community must develop tools for accurate assessment of CTID symptoms and guidelines for proactive management.

#### PRACTICE GUIDELINES DEVELOPMENT

In 1997, a group of clinicians specializing in oncology participated in a closed roundtable meeting. Based on their experience and expertise in the management of chemotherapy-induced diarrhea and their review of the published literature, panel members formulated comprehensive guidelines for the assessment and management of chemotherapy-induced diarrhea, which were published in 1998 by Wadler et al.<sup>10</sup> Subsequently, the same group published expanded guidelines that discussed in more detail the pathophysiology of secretory diarrhea and clinical issues surrounding accurate assessment of CTID.<sup>11</sup> In the process of revising the existing guidelines, a meeting was again convened in January 2002 to review the state of the art in the management of CTID. The current update seeks to broaden the guidelines originally established in 1998 to be inclusive of RT-induced diarrhea and to update and expand the recommendations based on data published since the original guidelines were developed.

#### METHODS

##### Panel Composition

The panel included 11 academic practitioners (see online Appendix) with backgrounds in medical oncology, radiation on-

cology, bone-marrow transplantation, gastroenterology, and endocrinology who have extensive experience and expertise in the management of CTID.

##### Process Overview

Panel members who participated in the original roundtable requested an unrestricted educational grant from Novartis Oncology (East Hanover, NJ) to convene the panel. Relevant literature published since 1998 was reviewed. Pertinent scientific evidence in the published literature was retrieved by searching MEDLINE (National Library of Medicine, Bethesda, MD). Key search terms included "radiation", "chemotherapy", "diarrhea", "octreotide", and "somatostatin analog". During the meeting, participants discussed the literature that they had reviewed, with particular emphasis on the findings of the independent review panel concerning early deaths in cooperative group trials of the IFL regimen.<sup>7</sup> Panel members also shared their professional experience and unpublished data from completed or ongoing studies. The previously published treatment algorithm was reviewed in detail, and recommendations for improvements and additions were discussed by the panel to achieve consensus. Recommendations for changes to the algorithm were later circulated to the panel members for review and to gain consensus.

##### Summary of Original Guidelines

The original guidelines were developed out of a recognition that there were no universally accepted, standardized recommendations for the comprehensive assessment and management of CTID. A critical initial step in defining an appropriate management plan for CTID is the accurate assessment of the onset and duration of diarrhea. However, a survey conducted by a working group of oncology nurses found that the assessment of diarrhea by the majority of respondents was limited to whether diarrhea was present or absent.<sup>12</sup> Further, the National Cancer Institute (NCI) Common Toxicity Criteria (version 2.0), which is the standard tool for assessing diarrhea severity (Table 1),<sup>13</sup> does not include assessment of duration of diarrhea, stool volume, and other co-existing symptoms that are predictive of life-threatening complications.<sup>14</sup> The original<sup>10</sup> and revised<sup>11</sup> guidelines address these important assessment issues.

With respect to management of chemotherapy-induced diarrhea, the original guidelines provide comprehensive recommendations on both nonpharmacologic (ie, dietary) and pharmacologic interventions. Based on evidence from well-controlled clinical trials, the opioid loperamide (4-mg initial dose followed by 2 mg every 4 hours) was recommended as the standard first-line therapy for chemotherapy-induced diarrhea.<sup>10</sup> High-dose loperamide (2 mg every 2 hours) has also been shown to be moderately effective in the control of chemotherapy-induced diarrhea associated with CPT-11.<sup>3,15,16</sup> In the face of uncontrolled NCI grade 1 or 2 diarrhea or grade 3 or 4 diarrhea, more aggressive therapy with the synthetic somatostatin analog, octreotide acetate, at a standard dose of 100 to 150  $\mu$ g three times daily (tid) via subcutaneous (SC) injection was recommended.<sup>10</sup>

#### NEW DEVELOPMENTS

##### Mortality Associated With the IFL Regimen

Recently, an independent panel of experts reviewed the cause of early toxic deaths among patients enrolled in two NCI-sponsored cooperative group trials of the IFL regimen:

**Table 1.** Common Toxicity Criteria (version 2.0) for Diarrhea

	Grade				
	0	1	2	3	4
Patients without colostomy	None	Increase of < 4 stools/day over pretreatment	Increase of 4-6 stools/day, or nocturnal stools	Increase of ≥ 7 stools/day or incontinence; or need for parenteral support for dehydration	Physiologic consequences requiring intensive care; or hemodynamic collapse
Patients with a colostomy	None	Mild increase in loose watery colostomy output compared with pretreatment	Moderate increase in loose watery colostomy output compared with pretreatment, but not interfering with normal activity	Severe increase in loose watery colostomy output compared with pretreatment, interfering with normal activity	Physiologic consequences requiring intensive care; or hemodynamic collapse

NOTE. Adapted from National Cancer Institute.<sup>13</sup>

North Central Cancer Treatment Group (NCCTG) Trial N9741 in patients with advanced metastatic colorectal cancer and Cancer and Leukemia Group B Trial C89803 (adjuvant trial).<sup>7</sup> In both of these trials, the IFL regimen was administered according to the Saltz protocol,<sup>8</sup> and there was an unusually high rate of early deaths (within 60 days) among patients in the IFL arm. In the NCCTG trial, there were 14 deaths (4.8%) among 289 patients in the IFL arm, and in the Cancer and Leukemia Group B T trial there were 14 deaths (2.2%) among 635 patients in the IFL arm. In both trials, the early death rate in the IFL arm was approximately two-fold higher than in the control arm and five-fold higher (with non-overlapping 95% CIs) than the 0.9% early death rate reported by Saltz et al.<sup>8</sup> The increase in treatment-related deaths was of particular concern because patients in C89803 receiving potentially curative adjuvant therapy for Dukes' stage III colon cancer were also at risk. These findings prompted both trials to suspend further patient accrual and prompted a review of the early deaths by an independent panel of five medical oncologists.<sup>7</sup>

The findings of the independent panel were that most of these deaths resulted from GI toxicity and cardiovascular events, and the panel recommended that a higher degree of vigilance is needed with regard to monitoring GI toxicity, management of chemotherapy-induced diarrhea, and appropriate dose modifications (or discontinuation of therapy) in future patients treated with IFL. These recommendations highlighted the need for comprehensive guidelines for assessment and management of chemotherapy-induced diarrhea.

### Gastrointestinal Syndrome

One of the most important outcomes of the independent panel's review of these deaths is the recognition that the majority of deaths among patients treated with the IFL regimen resulted from a GI syndrome, defined as a constellation of symptoms including severe diarrhea, nausea, vomiting, anorexia, and abdominal cramping. These symptoms were often associated with severe dehydration, neutrope-

nia, fever, and electrolyte imbalances. In particular, the presence of severe abdominal cramping appears to be an important early warning sign of imminent diarrhea. Of note, the GI syndrome is not limited to patients receiving IFL. Other regimens including high-dose leucovorin plus FU can produce a similar spectrum of symptoms.

### Recommendations

Based on their findings, Rothenberg et al<sup>7</sup> made several specific recommendations that apply to patients receiving the IFL regimen and that are relevant to general guidelines for managing chemotherapy-induced diarrhea. First, they stressed the need for more stringent monitoring of patients receiving IFL and other intensive combination regimens. The independent panel recommended weekly assessment of GI toxicity at least during the first cycle of therapy, particularly for older patients. Blood tests should be performed no more than 48 hours before scheduled treatment to assess neutropenia and changes in electrolytes. Second, the independent panel recommended more aggressive management of patients who experience diarrhea, either in isolation or as part of the GI syndrome. This includes use of oral antibiotics if diarrhea persists for more than 24 hours. The independent panel supported consideration of an approach taken in Europe as outlined in Table 2.<sup>7</sup> Finally, the independent panel recommended that IFL should be discontinued or withheld from any patient experiencing significant chemotherapy-induced diarrhea until complete resolution of symptoms for at least 24 hours without anti-diarrheal therapy. These recommendations should not be limited to patients receiving IFL, but should be followed for any patient with chemotherapy-induced diarrhea.

### Optimal Dose of Octreotide

Early studies of octreotide for chemotherapy-induced diarrhea investigated SC doses ranging from 50 to 100 µg twice daily or tid.<sup>11</sup> Although the optimal dose of octreotide has not been determined, recent data suggest that higher doses may be more effective. A dose-escalation study with

**Table 2.** Specific Recommendations of the Independent Panel for Management of Chemotherapy-Induced Diarrhea in Patients Receiving the IFL Regimen<sup>7</sup>

Clinical Presentation	Intervention
Diarrhea, any grade	Oral loperamide (2 mg every 2 hours); continue until diarrhea-free for $\geq 12$ hours
Diarrhea persists on loperamide for $> 24$ hours	Oral fluoroquinolone $\times 7$ days
Diarrhea persists on loperamide for $> 48$ hours	Stop loperamide; hospitalize patient; administer IV fluids
ANC $< 500$ cells/ $\mu\text{L}$ , regardless of fever or diarrhea	Oral fluoroquinolone (continue until resolution of neutropenia)
Fever with persistent diarrhea, even in the absence of neutropenia	Oral fluoroquinolone (continue until resolution of fever and diarrhea)

Abbreviations: IFL, irinotecan plus bolus fluorouracil/leucovorin; IV, intravenous; ANC, absolute neutrophil count.

octreotide doses up to 2,500  $\mu\text{g}$  tid in patients receiving FU or a modified FU regimen showed that resolution of diarrhea and patients' ability to complete chemotherapy increased with higher octreotide doses.<sup>4</sup> In addition, Gebbia et al<sup>17</sup> compared 500  $\mu\text{g}$  octreotide tid with loperamide (4 mg tid) in patients receiving modulated FU regimens and demonstrated a significant improvement in the rate of diarrhea resolution after 4 days (80% with octreotide  $\nu$  30% with loperamide;  $P < .001$ ). Recently, Barbounis et al<sup>18</sup> demonstrated that octreotide at a dose of 500  $\mu\text{g}$  tid was effective in patients receiving CPT-11 who had loperamide-refractory diarrhea. Goumas et al<sup>19</sup> have reported the only prospective comparison of 100  $\mu\text{g}$  versus 500  $\mu\text{g}$  octreotide tid in 59 patients with  $\geq$  grade 3 chemotherapy-induced diarrhea who had failed loperamide (4 mg tid) for at least 48 hours. Treatment with 500  $\mu\text{g}$  octreotide was significantly more effective than 100  $\mu\text{g}$  (90%  $\nu$  61% of patients had complete resolution of diarrhea;  $P < .05$ ), and both doses were well tolerated. Unfortunately, a randomized Inter-group trial comparing high-dose octreotide (1,500  $\mu\text{g}$  tid) with standard-dose octreotide (150  $\mu\text{g}$  tid) and standard-dose loperamide never completed accrual. These data suggest that 500  $\mu\text{g}$  octreotide tid may be more effective than lower doses in patients who fail loperamide. Overall, the data support upward titration of the octreotide dose until symptoms are controlled.<sup>20</sup>

### Role of Prophylactic Antidiarrheal Therapy

Because of the well-recognized risk of diarrhea associated with CPT-11, several recent studies have investigated various prophylactic regimens to prevent chemotherapy-induced diarrhea. Takeda et al<sup>21</sup> reported the success of oral alkalization of the intestinal lumen in conjunction with control of defecation. In contrast, a randomized trial of oral racecadotril (Tiorfan; Bioprojet Pharma, Paris, France), at a dose of 100 mg tid for 15 days concurrent with administration of CPT-11, failed to demonstrate any effect on the incidence of diarrhea compared with placebo.<sup>22</sup> Similarly disappointing results were reported from a single-arm study of prophylactic octreotide (150  $\mu\text{g}$  twice daily) in patients treated with FU plus high-dose leucovorin on the Roswell Park schedule.<sup>23</sup> Recently, a long-acting, slow-release formulation of octreotide (octreotide LAR) has been

developed that can be administered by intramuscular injection once a month. Once steady-state levels have been achieved, a 20-mg intramuscular dose of octreotide LAR every 4 weeks produces the same pharmacologic effects as 150  $\mu\text{g}$  octreotide tid by SC injection<sup>24,25</sup> and dramatically reduces fluctuations in peak and trough octreotide concentrations.<sup>25</sup> Octreotide LAR (at a starting dose of 20 mg) effectively controls diarrhea associated with carcinoid syndrome,<sup>24</sup> and monthly doses of 20 to 30 mg are currently being investigated for the treatment and prevention of chemotherapy-induced diarrhea. In the future, it may also be possible to prevent chemotherapy-induced diarrhea associated with CPT-11 by using specific modulators of intestinal SN-38 (the active metabolite of CPT-11). These strategies will require further investigation.

### Radiation Therapy-Induced Diarrhea

Pelvic or abdominal RT causes acute enteritis characterized by abdominal cramping and diarrhea in approximately 50% of treated patients, and the incidence is higher with concomitant chemotherapy.<sup>26,27</sup> Symptoms typically occur during the third week of fractionated RT.<sup>28</sup> Oral opiates, including loperamide and diphenoxylate, are effective in the majority of patients with mild symptoms and are the standard therapy. However, a randomized trial of SC octreotide (100  $\mu\text{g}$  tid) versus oral diphenoxylate (10 mg/d) in 61 patients with grade 2 or 3 diarrhea has demonstrated that octreotide is significantly more effective than oral opiates.<sup>29</sup> Diarrhea completely resolved within 3 days in 61% of patients treated with octreotide versus only 14% of patients treated with diphenoxylate ( $P < .002$ ).

Several clinical trials have focused on prevention of diarrhea in patients receiving pelvic RT. Sucralfate, a non-systemically absorbed aluminum hydroxide complex, has been the most widely investigated agent. However, several randomized, placebo-controlled clinical trials have yielded mixed results. Three European trials have demonstrated significant decreases in the occurrence of diarrhea in patients receiving 1 to 2 g sucralfate (two to six times daily) during pelvic RT compared with placebo.<sup>30-32</sup> One of these trials, conducted in Sweden, also showed a significant decrease in long-term bowel dysfunction (based on stool frequency 12 to 14 months after RT) in patients treated with

sucralfate.<sup>31</sup> In contrast, results of an NCCTG trial and an Australian trial showed no improvement in diarrhea and significant worsening of some GI symptoms among patients receiving sucralfate compared with placebo.<sup>26,33</sup> These findings are consistent with several other studies investigating the use of sucralfate to mitigate mucosal toxicity associated with cancer treatment. These studies have consistently failed to demonstrate a beneficial effect of sucralfate and have also documented increases in some GI toxicity.<sup>34-36</sup> Taken together, the results suggest that sucralfate is not effective in preventing RT-induced diarrhea and may aggravate some GI symptoms.

Salicylates, including sulfasalazine and olsalazine, also have been investigated for prevention of RT-induced diarrhea based on the hypothesis that prostaglandins play a role in the pathophysiology of diarrhea. One study suggested that sulfasalazine may be effective in this setting,<sup>37</sup> whereas olsalazine dramatically increased diarrhea compared with placebo.<sup>38</sup> These contradictory findings are surprising in view of the identical putative mechanisms of action of the two drugs. Until a confirmatory trial is conducted, sulfasalazine should not be used outside of a clinical trial in patients receiving pelvic RT. To date, there does not appear to be any clearly effective pharmacologic strategy for prevention of RT-induced diarrhea. However, octreotide is currently being investigated in this setting.

#### REVISED RECOMMENDATIONS

Based on review of all the available data, the panel revised the existing algorithm for assessment and management of CTID. Significant changes from the previously published guidelines are indicated in bold italic type. The key elements of the proposed algorithm for CTID are shown in Figure 1.<sup>11</sup>

#### Assessment

**Recommendation.** Assessment of symptoms needs to be rigorous and should include duration of symptoms, constellation of signs and symptoms, and severity of symptoms. Assess number of stools over baseline and stool composition, including presence of nocturnal diarrhea. Assess presence of added risk factors: fever, orthostatic symptoms (eg, dizziness), abdominal pain/cramping, or weakness. Stool volume is a valuable piece of information, but it may be impractical in most clinical settings. In addition, the patient's hydration status should be assessed by physical examination.

#### Determining the Appropriate Management of CTID

**Recommendation:** The patient's constellation of symptoms should be classified as either "uncomplicated" or "complicated", and this will determine the most appropriate course of action. Patients with grade 1 or 2 diarrhea with no other complicating signs or symptoms listed below may be classified as "uncomplicated" and managed conservatively.

However, if a patient with grade 1 or 2 diarrhea has any one of the following added risk factors: moderate to severe cramping,  $\geq$  grade 2 nausea/vomiting, decreased performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration, he or she should be evaluated further and monitored closely. These patients should be classified as "complicated" and may require more aggressive management. Any patient with grade 3 or 4 diarrhea would be classified as "complicated" and require aggressive management.

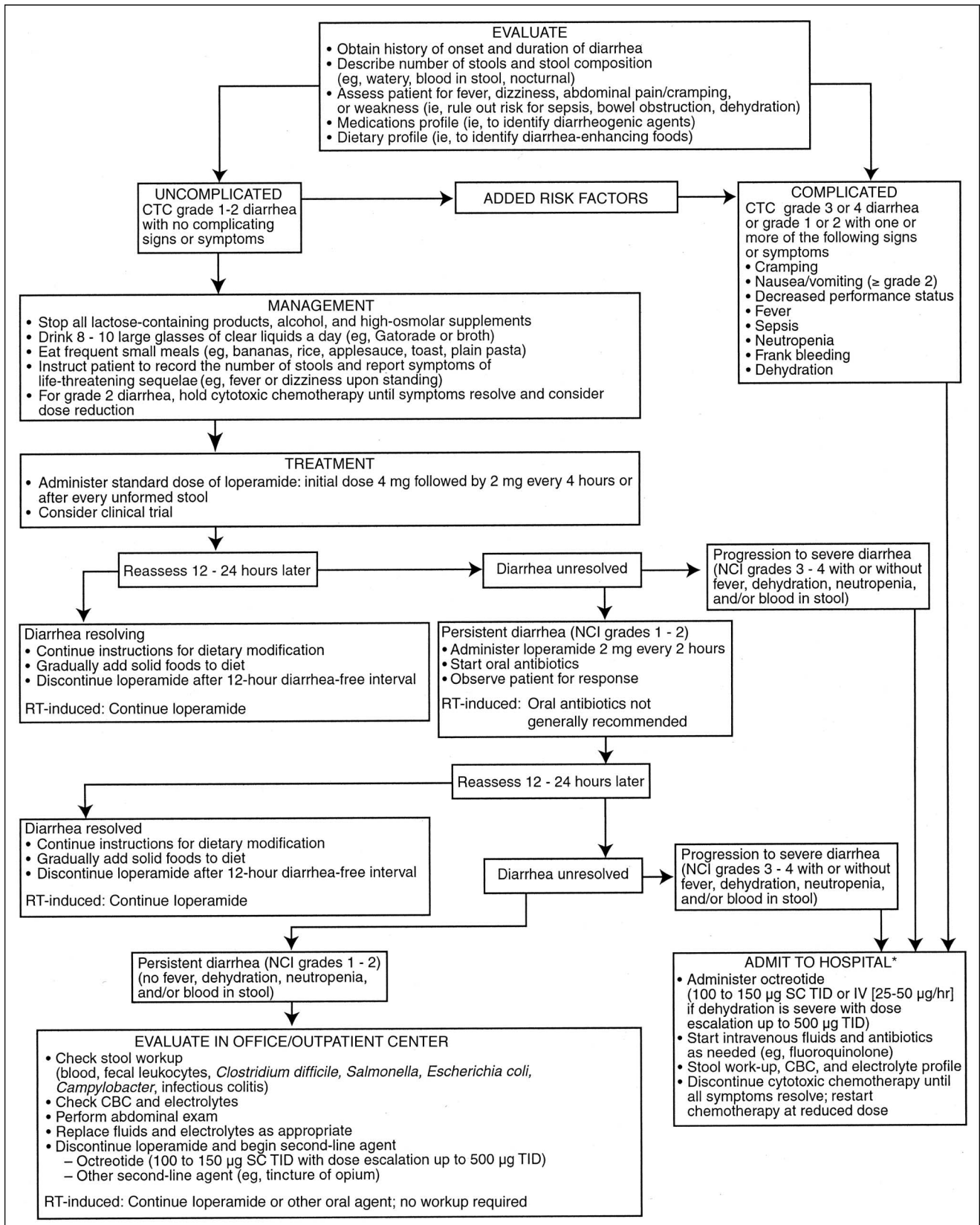
In light of the recent appreciation of the potential for life-threatening complications arising from the GI syndrome associated with the IFL regimen, the existing guidelines have been revised to reflect the need to recognize the early warning signs of complicated cases of CTID that require more aggressive management. For example, severe cramping is often a harbinger of severe diarrhea, and fever may indicate infectious complications. This will require education of physicians, nurses, and patients about what to expect and what to look for during treatment.

#### Aggressive Management of Complicated Cases

**Recommendation:** Aggressive management of complicated cases should involve intravenous (IV) fluids; octreotide at a starting dose of 100 to 150  $\mu$ g SC tid or IV (25 to 50  $\mu$ g/h) if the patient is severely dehydrated, with dose escalation up to 500  $\mu$ g until diarrhea is controlled, and administration of antibiotics (eg, fluoroquinolone). This may require admission to the hospital; for select patients, diarrhea may be managed with intensive home nursing or in a day hospital. Stool work-up (evaluation for blood, fecal leukocytes, *C difficile*, *Salmonella*, *E coli*, *Campylobacter*, and infectious colitis), complete blood count, and electrolyte profile should be performed. This may not be appropriate for RT-induced diarrhea. Any patient with chemotherapy-induced diarrhea who progresses to grade 3 or 4 diarrhea after 24 or 48 hours on loperamide should also be treated as described above. Continue intervention as described until the patient has been diarrhea-free for 24 hours.

These recommendations for the aggressive management of complicated cases of chemotherapy-induced diarrhea are based on evidence that the GI syndrome is an indicator that the patient may be at serious risk for dehydration and/or infection and other potentially life-threatening complications. Moreover, loperamide, even at high-doses, may be less effective in patients with grade 3 or 4 diarrhea.<sup>39</sup> Therefore, it is appropriate to start immediate octreotide therapy (either SC or IV if the patient is already severely dehydrated) along with antibiotics.

**Management of severe radiation therapy-induced diarrhea.** For patients presenting with a complicated case of RT-induced diarrhea, it may not be necessary to hospitalize the patient. The treating physician should consider hospitalization or, alternatively, intensive home care nursing or management in an outpatient facility able to provide a high



**Fig 1.** Proposed algorithm for the assessment and management of treatment-induced diarrhea. \*For radiation-induced cases and select patients with CID, consider intensive outpatient management, unless the patient has sepsis, fever, or neutropenia. CTC, Common Toxicity Criteria; NCI, National Cancer Institute; RT, radiotherapy; SC, subcutaneous; tid, three times per day; IV, intravenous; CBC, complete blood count; CID, chemotherapy-induced diarrhea. Adapted with permission from Kornblau et al<sup>11</sup>.

level of care and monitoring such as an outpatient infusion therapy unit. The patient's constellation of symptoms should be considered to determine if it is appropriate to treat with octreotide and IV antibiotics and whether it is necessary to do a complete stool and blood work-up. IV antibiotics might worsen symptoms in some cases, and patients with grade 3 or 4 diarrhea, but no other complicating signs or symptoms, may not require octreotide.

### **Management of Uncomplicated Mild to Moderate Diarrhea**

**Recommendation.** Initial management of mild to moderate diarrhea should include dietary modifications (eg, eliminating all lactose-containing products and high-osmolar dietary supplements), and the patient should be instructed to record the number of stools and report symptoms of life-threatening sequelae (eg, fever or dizziness on standing). Loperamide should be started at an initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool (not to exceed 16 mg/d).<sup>40</sup> Patients should also be considered for clinical trials of new oral antidiarrheal agents.

**If mild to moderate diarrhea resolves.** If diarrhea resolves with loperamide, the patients should be instructed to continue dietary modifications and to gradually add solid foods to their diet. In the case of chemotherapy-induced diarrhea, patients may discontinue loperamide when they have been diarrhea-free for at least 12 hours. However, in the case of RT-induced diarrhea, patients should be instructed to continue taking standard doses of loperamide for the duration of RT. Because of the long duration of fractionated RT, there is potential for repeated injury to the intestinal mucosa resulting in enteritis.

**If mild to moderate diarrhea persists.** If mild to moderate diarrhea persists for more than 24 hours, the dose of loperamide should be increased to 2 mg every 2 hours, and oral antibiotics may be started as prophylaxis for infection.

This recommendation is consistent with those published by Rothenberg et al<sup>7</sup> based on the review of the early deaths in the NCI trials associated with the IFL regimen (Table 2). Patients with persistent diarrhea are at increased risk for infection; therefore, oral antibiotics may prevent infectious complications.

**If mild to moderate diarrhea persists for more than 48 hours on loperamide.** If mild to moderate chemotherapy-induced diarrhea has not resolved after 24 hours on high-dose loperamide (48 hours total treatment with loperamide), it should be discontinued and the patient should be started on a second-line antidiarrheal agent such as SC octreotide (100- to 150- $\mu$ g starting dose, with dose escalation as needed) or other second-line agents (eg, oral budesonide or tincture of opium). In the case of chemotherapy-induced diarrhea, the patient should be seen in the physician's office or outpatient center for further evaluation, including complete stool and blood work-up.

Stool work-up should include evaluation for pathogens. Fluids and electrolytes should be replaced as needed. However, in the case of RT-induced diarrhea, it may be appropriate in this situation to continue treatment with loperamide, and a complete work-up may not be necessary.

There is recent evidence, as described above, that octreotide is effective following failure of treatment with loperamide.<sup>18,19</sup> There is also some preliminary evidence from a phase I study that budesonide may be effective in this setting.<sup>41</sup> In addition, although there are no reports in the literature demonstrating the efficacy of tincture of opium for the treatment of chemotherapy-induced diarrhea, it is a widely used antidiarrheal agent and may be a reasonable alternative as second-line therapy. It is important to note, however, that the best preparation is deodorized tincture of opium, which contains the equivalent of 10 mg/mL morphine. The recommended dose of deodorized tincture of opium is 10 to 15 drops in water every 3 to 4 hours.<sup>42</sup> Alternatively, paregoric (ie, camphorated tincture of opium) can be prescribed. This is a less-concentrated preparation that contains the equivalent of 0.4 mg/mL morphine. The recommended dose is 1 teaspoon (5 mL) in water every 3 to 4 hours.<sup>42</sup> Because of the differences in morphine content, care must be taken not to confuse these two preparations.

**Recommendation:** *If mild to moderate RT-induced diarrhea has not resolved after 24 hours on high-dose loperamide, continue loperamide (2 mg every 2 hours) and consider further evaluation in office or outpatient center.* In patients with persistent mild to moderate diarrhea during RT, it may be appropriate to continue loperamide therapy or another oral antidiarrheal agent. In the majority of cases, it may not be appropriate to prescribe SC octreotide. It also may not be necessary to do a complete stool and blood work-up unless there are signs of dehydration or infection. The patient's constellation of symptoms should determine if he or she requires further evaluation and whether to initiate more aggressive antidiarrheal therapy.

## **DISCUSSION**

Recent findings with respect to the potential for life-threatening complications of diarrhea in colorectal cancer patients receiving the IFL regimen have highlighted the importance of careful monitoring and early identification of signs and symptoms that indicate a complicated case with a greater risk of severe and life-threatening sequelae. These early warning signs indicate that a patient may require aggressive therapy with octreotide and early use of antibiotics. Although there are no definitive data yet on the role of prophylactic antidiarrheal therapy, several promising agents are being investigated. It is hoped that, with the adoption of standard practices for assessment and management of CTID, morbidity and mortality can be reduced.

## Appendix

The appendix is included in the full-text version of this article, available on-line at [www.jco.org](http://www.jco.org). It is not included in the PDF (via Adobe® Acrobat Reader®) version.

## Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant

within the last 2 years: Al B. Benson III, Pfizer, Novartis; Edith P. Mitchell, Pfizer, Sanofi, Bristol-Myers Squibb; Thomas M. O'Dorisio, Novartis; Everett E. Vokes, CV Vision, Novartis. Performed contract work within the last 2 years: Al B. Benson III, Pfizer, Novartis; Edith P. Mitchell, Roche, Pfizer, Sanofi, Bristol-Myers Squibb, Novartis; Thomas M. O'Dorisio, Novartis. Received more than \$2,000 a year from a company for either of the last 2 years: Jaffer A. Ajani, Novartis; Al B. Benson III, Pfizer, Novartis; Edith P. Mitchell, Pfizer, Sanofi, Bristol-Myers Squibb, Ortho-Biotech, Novartis.

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