

Preventing and Treating Diarrhea Related to Chemotherapy and/or Radiation Therapy

Evidence Table

(Literature search completed through May 2008)

Author and Year	Characteristics of the Intervention	Sample Characteristics, Setting Characteristics, Study Design, and Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions and/or Contraindications, Special Training Needs, and Costs
Octreotide For Treatment of Chemotherapy-Induced Diarrhea: PEP Weight of Evidence Category: Recommended for Practice					
Zidan, 2001	<p>Octreotide 100mcg SQ 3x/day for three days followed by 50mcg 3x/day for three days Octreotide used for treatment of severe CID refractory to loperamide</p> <p>Median time between chemotherapy and starting octreotide was 8 days (range 5-9 days)</p>	<p>Prospective study of 32 patients from 2 cancer centers with grade 2/3 CID (WHO) refractory to loperamide who had received various regimens containing: 19 pts-5-FU/leucovorin 4pts- Irinotecan 5-FU/leucovorin 8 pts 5-FU- combination including one or more of cyclophosphamide, epirubicin, cisplatin, methotrexate, and cisplatin 1 pt - plus RT</p> <p>Primary tumors: Colorectal- 23 Gastric- 3 Other-6</p> <p>Loperamide tx: 4mg initially and then 2mg q6hours x 48 hours</p>	<p># of bowel movements</p> <p>CR= complete response</p> <p>PR= 1-2 diarrheal stools/day</p> <p>No Response= 3 or more diarrheal stools/day</p> <p>Progression= increase in # of diarrheal stools</p>	<p>CR=94% in 30/32 pts 5 w/in 24 hours 14 w/in 48 hours 11 w/in 72 hours</p> <p>Octreotide is highly effective as second line therapy in pts with CID</p> <p>12 pts in complete response discontinued tx after 3 days because "they felt very healthy"</p>	<p>Very small study</p> <p>No toxic side effects documented</p> <p>High response rate</p>
Octreotide for the Treatment of Chemoradiotherapy-Induced Diarrhea: ONS PEP Weight of Evidence Category: Likely to be Effective					
Topkan & Karaoglu, 2006	<p>Patients with rectal carcinoma who have grade 2-3 diarrhea received 150 mcg octreotide SQ tid once they were unresponsive to oral loperamide administration (4 mg tid for 48 hours).</p> <p>All patients received hydration and were advised to consume a low fiber/lactose diet</p>	<p>N = 42 Grade 3-4 diarrhea associated with 5-FU administration during whole pelvic RT</p> <p>Prospectively designed</p> <p>Diarrhea had to occur following at least one course of 5-FU during pelvic RT Maximum days of octreotide treatment = five days If patients had progressive improvement of chemoradiotherapy-induced diarrhea (CRTID) during the five days of treatment, but not a complete response (CR),</p>	<p>1. Complete resolution of CRTID. 2. Prevention of treatment delays attributed to diarrhea.</p> <p>Complete resolution of diarrhea equals success</p>	<p>Median duration of diarrhea prior to first dose of octreotide was 78 hours</p> <p>Most cases of diarrhea were diagnosed in the first four weeks</p> <p>Median time to 1st dose of octreotide acetate was 19 days (range)</p> <p>Octreotide was well tolerated by all patients Complete resolution of diarrhea was achieved in 34 of 42 patients during planned treatment period (five days)</p>	<p>Small sample size</p> <p>Difficult to generalize (rectal carcinoma only)</p> <p>No statistical significance reported</p> <p>Descriptive results only</p>

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		<p>chemoradiotherapy (CRT) was discontinued and octreotide prolonged for three additional days</p> <p>Refractory to loperamide</p>		<p>Average time to CR was 2.7 days</p> <p>No treatment delay reported in 34 patients who responded to subcutaneous octreotide administration</p> <p>CRT was delayed an average of 7.7 days in the eight unresponsive patients.</p> <p>Those with CR were able to be treated as outpatients; non-responders required hospitalization</p>	
<p>Octreotide for the Treatment of Chemotherapy-Related Diarrhea: PEP Weight of Evidence Category: Likely to be Effective</p>					
<p>Rosenoff et. al., 2006</p>	<p>124 evaluable patients randomly assigned to a 30mg or 40mg octreotide dose group. First dose of octreotide given IM 7-14 days prior to day#1 of next chemo cycle. Second dose coincided with chemotherapy cycle. Subsequent cycles delivered q 28 days up to a total of 6 doses on a schedule independent of the chemo cycles.</p> <p>Test dose of octreotide 100 micrograms SQ before initiation of octreotide LAR to determine intolerance to octreotide</p>	<p>Open Label, randomized multi-center-parallel group design to compare the efficacy of two dose levels of octreotide LAR in preventing CID in patients with active or prior CID</p> <p>the two treatment groups similar in current chemotherapy regimens, severity of most recent diarrhea episode, body weight, primary tumor type, and proportion of pts with colostomy prior to study entry- 57% of pts txed 5fu based regimen with/without irinotecan,leucovoran, or oxaliplatin, 25% irinotecan regimens with /without 5fu,leucovoran, or oxaliplatin,Primary tumor types colorectal 75%,breast 7%,lung 6%,hematologic 1%, other 10%</p>	<p>Patient diaries collected on monthly basis to obtain data for diarrhea assessment, concomitant meds, adverse events, and utilization of health care resources.</p> <p>Health-related quality of life (QOL) assessed at baseline and at the end of study visit using modified Functional Assessment of Chronic Illness Therapy-Diarrhea(FACIT_D) scale</p> <p>Investigators collected data from the Treatment Satisfaction Questionnaire for Medication for Chemotherapy Induced Diarrhea (TSQM-CID), aversion of the previously validated TSQM, at baseline for loperamide and diphenoxylate and at the end of study visit for octreotide LAR</p> <p>1° endpoint- proportion of patients experiencing severe diarrhea 2° endpoint- (NCI grade 3 or 4) proportion of patients requiring IV</p>	<p>Fewer patients experienced severe diarrhea, required iv fluid, or had unscheduled diarrhea related healthcare visits with the 40mg group</p> <p>However the difference did not reach a statistical difference, no significant recommendations can be made</p> <p>1° primary proportion of patients who experienced severe diarrhea (grade 3 or 4) during the study 61.7% in 30mg group and 48.4% in 40mg group (p=0.14)</p> <p>2°- Fewer patients in the 40mg group required IV fluid (p=0.11), had unscheduled diarrhea related healthcare visits (p=0.11). Changes in primary therapy as a result of diarrhea was 61.7% in the 30mg group and 64.1% in the 40mg group (p=0.78). However the difference did not reach a statistical difference</p>	<p>Weakness- no comparison between daily tid octreotide and octreotide LAR</p> <p>Significantly greater proportion of females in 30mg group(sensitivity analysis showed no need to adjust for gender)</p> <p>No specific recommendations regarding superiority of 30mg versus 40mg can be made</p>

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			fluids, unscheduled provider visits, changes in primary therapy due to diarrhea. Treatment satisfaction and QOL		
Rosenoff, 2004	Octreotide Long acting (LAR) 20-30 mg once monthly IM injection as secondary prophylaxis (every 28 days); one pt received 40 mg with decrease back to 30 mg This was given once pts failed loperamide plus/minus lomotil.	N=11 Case studies All pts developed Grade 3-4 diarrhea secondary to receiving adjuvant therapy (5-FU/LV, CPT-11 or gefitinib or low dose 5FU/pelvic irradiation)	Resolution of diarrhea QOL evaluation	Most effective dose appears to be 30mg octreotide LAR Resolution of diarrhea within 24 hours to 4 weeks after 30mg dose Prophylactic use every 28 days prevented further significant development of diarrhea (intermittent grade 1 diarrhea occurred; relief obtained with opioid therapy) Octreotide LAR may have value as secondary prophylaxis for prevention of CID in subsequent chemo cycles Improved QOL by decreasing abdominal cramping and diarrhea	Cost effective in preventing need for hospitalization and additional patient care. Convenience of monthly injections vs. several daily injections Allowed continuation of full-dose therapy on schedule Small sample size QOL instrument not validated/not stated it is validated in this summary
Octreotide for Treatment of Radiation-Induced Diarrhea: ONS PEP Weight of Evidence Category: Likely to be Effective					
Yavuz, 2002	Patients were randomized to receive either 100 mcg SQ tid of octreotide or 2.5 mg po qid of diphenoxylate/atropine	n=61 patients with grade 2-3 diarrhea associated with Pelvic XRT octreotide group = 33 diphenoxylate group = 28 sample was balanced for clinical characteristics (including radiation dose)	# of days to resolution of diarrhea # of days of interruption of radiation therapy Success = complete response within 3 days	The octreotide group had resolution of diarrhea in 3.3 days compared with 5.6 in the diphenoxylate group (p=0.0001) The octreotide group had 0.45 days of interrupted radiotherapy compared with 1.89 days in the diphenoxylate group (p=0.003) Success: Octreotide = 61% Diphenoxylate = 14% (p=0.002)	Small sample size but promising results

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Probiotics For Prevention of Radiation-Induced Diarrhea: PEP Weight of Evidence Category: Likely to Be Effective					
Delia et al, 2007	<p>Examined effect of probiotic use for prevention of radiation-induced diarrhea. Experimental group: high-potency probiotics (VSL#3 one sachet TID) vs. placebo group (identical appearing sachet).</p> <p>Note: VSL #3 contained 450 billions/gm of viable lyophilized bacteria, including 4 strains of lactobacilli (<i>L. casei</i>, <i>L. plantarum</i>, <i>L. acidophilus</i> and <i>L. delbruekii</i> subsp. <i>Bulgaricus</i>); 3 strains of bifidobacteria (<i>B. longum</i>, <i>B. breve</i> and <i>B. infantis</i>) and 1 strain of streptococcus salivarius subsp. <i>Thermophilus</i>.</p>	<p>Double blind, randomized, placebo-controlled trial. N=490 s/p adjuvant post-op radiation therapy after surgery for sigmoid, rectal or cervical cancer.</p> <p>Experimental group received high-potency probiotics (VSL#3) daily from first day of radiation therapy until the end of scheduled cycles. Control group received an identical appearing placebo.</p>	<p>Efficacy endpoints included incidence and severity of radiation induced diarrhea; daily # of BM's; time from start of study until need for loperamide.</p> <p>Endpoints (clinical symptoms, use of medications and any adverse events) were reviewed with patients weekly during scheduled radiation therapy treatments and again 1 month after completion.</p>	<p>97.5% of placebo and 99.1% of experimental participants completed study</p> <p>More patients in the placebo group had radiation-induced enteritis and colitis (P<0.001) Placebo had more severe toxicity (grade 3 or 4) (p<0.001); mean daily number of BM higher for placebo (p<0.001)</p> <p>Conclusion: Use of a probiotic lactic-acid producing bacteria is a safe, easy, feasible approach to preventing radiation-induced diarrhea after surgery for abdominal and pelvic cancer.</p>	<p>Severity assessed using WHO standards, therefore deviates from other studies which use NCI standards.</p> <p>Prevention for radiation induced diarrhea only. Does not address safety in neutropenic patients.</p> <p>Strengths: safe for use in radiation treatment population; no cases of bacteremia, sepsis or septic shock; causal mechanism known (lactobacilli lower the production of proinflammatory cytokines and other effectors of inflammation and tissue injury; probiotic bacteria up-regulate the innate immune response in the gut and protect against invasive organisms)</p> <p>Need further studies on different probiotic preparations/mixtures</p>
Urbanscek et al, 2001.	<p>Objective of the study: to determine the efficacy and tolerability of <i>Lactobacillus rhamnosus</i> (marketed as <i>Antibiophilus</i>) in treating radiation-induced diarrhea.</p>	<p>Study design: randomized, double-blind, parallel group</p> <p>Both groups were instructed to use 3 sachets per day. Treatment group: <i>Antibiophilus</i> sachets (each sachet contained 1.5 grams of <i>Lactobacillus rhamnosus</i>) vs Control group: identical appearing placebo (contained 700 mg corn starch, 797 mg microcrystalline cellulose, 1.37 mg iron oxide, 1.13 mg orange coloring agent, 1 mg caramel aroma). Both groups were asked to document date and time of rescue medications.</p> <p>Study population: cancer patients</p>	<p>Primary endpoint to assess efficacy: time to and frequency of rescue medication for diarrhea</p> <p>Secondary endpoints: number of bowel movements; diarrhea grading (0 for non; 1 for mild; 2 for moderate and 3 for severe)</p>	<p>A greater percentage of patients in the control group required rescue medication (48% control group vs 35% of experimental group), but the difference was not statistically significant (p=0.064)</p> <p>Secondary endpoints: Number of bowel movements: greater number per day for control group (3.2 vs 2.4) but not statistically significant (p<.10)</p> <p>Diarrhea grading: greater severity for control group (1 vs 0.7) but not statistically significant</p>	<p>Strengths: Randomized, double-blinded, controlled study</p> <p>Large study population.</p> <p>Limitations: Study population was limited to patients who were already experiencing diarrhea (i.e. treatment vs prevention)</p> <p>Endpoints were measured with subjective report by patient</p>

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		<p>between 19-75 years of age, who developed diarrhea within 4 weeks of receiving radiation therapy to the abdomen.</p> <p>--Experimental group: 102 patients</p> <p>--Control group: 103 patients</p>		<p>Authors' conclusions: results suggest a superior efficacy for diarrhea treatment among experimental group, yet results failed to show a statistically significant difference for any of the measured variables. Despite the lack of statistically significant differences, the authors conclude that Antibiophilus therapy yielded a favorable benefit to risk ratio.</p>	
Psyllium Fiber For Prevention of Radiation-Induced Diarrhea: PEP Weight of Evidence Category: Likely to be Effective					
Murphy et al., 2000	<p>Randomized controlled trial (not blinded) studying the effectiveness of 1-2 teaspoons Metamucil (psyllium fiber) taken during pelvic radiation treatment for prostate or gynecological cancer, was effective in reducing the incidence and/or severity of radiation-induced diarrhea. The experimental group received the Metamucil, versus control group (no Metamucil supplements).</p> <p>Both groups received a booklet titled "Nutritional Guidelines to Help Control Diarrhea."</p>	<p>N=84 (72 males; 12 females)</p> <p>Population: patients with prostate or gynecologic cancer undergoing radiotherapy to the pelvis of at least 4000 cGy in 20 fractions. Excluded patients with GI disease, tumor of the GI tract, or patients regularly using laxatives or anti-diarrheal meds.</p> <p>Design: Patients kept diaries from day 1 of recruitment through 28 days post-treatment, recording number of bowel movements/day, consistency of stools, amt of anti-diarrhea medication taken, daily dose of Metamucil for experimental group)</p>	<p>Assessed diarrhea using Murphy Diarrhea Scale (scale not yet validated but based on pre-existing scales)</p> <p>Day with diarrhea defined as any 1 of the following: (a) 4-6 BM more than nL for pt (b) 1+ watery BMs (c) 2-3 loose BM more than nL for pt (d) use of anti-diarrhea meds</p> <p>Severity rankings: Mild: <11% days with diarrhea Moderate: 11-20% days with diarrhea Severe: >20% days with diarrhea</p> <p>Endpoints: Mean severity score for diarrhea; incidence of diarrhea; mean time to onset of diarrhea; mean duration of diarrhea (in days); mean % days took anti-diarrhea medication</p>	<p>Statistically significant difference in severity of diarrhea (p=0.030)</p> <p>Statistically significant difference in incidence of diarrhea (p=0.049)</p> <p>No statistic difference in mean time to onset of diarrhea, duration of diarrhea, % days took anti-diarrhea meds.</p> <p>Metamucil well-tolerated by patients with no complaints of GI side effects</p> <p>Metamucil low cost</p> <p>Conclusion: Psyllium fiber is effective to reduce the incidence and/or severity of radiation-induced diarrhea in patients undergoing pelvic radiation treatment for prostate or gynecological cancer.</p>	<p>LIMITATIONS</p> <p>Pilot study, therefore limited in scope</p> <p>High attrition rate (60 completed study; 30 in each group; patients with inaccurate or incomplete diaries, or use of Metamucil while in non-metamucil group were excluded from final analysis)</p> <p>Proctor and Gamble, manufacturer of Metamucil, provided partial funding for the study (research grant)</p> <p>STRENGTHS</p> <p>Intervention was well-tolerated and low-cost</p>
Amifostine For Treatment Of Chemotherapy-Induced Diarrhea: ONS PEP Weight of Evidence Category: Benefits Balanced With Harms					
Tsavaris et al, 2003	<p>Amifostine 800 mg/m2 infusion during 5-Fu and calcium folinate infusion when diarrhea recurred.</p>	<p>N=52 pts recruited consecutively with CRC</p> <p>Eligible pts had advanced metastatic or stage Dukes B2 or C</p>	<p>Continuous outcomes were compared using paired t-test (comparisons with baseline) or the independent sample t-test (between groups). Changes in</p>	<p>Mean number of cycles of chemo administered prior to amifostine was 6.55 ± 2.83 and median 9 (range 5-17).</p>	<p>Amifostine side effects include hypotension, nausea, vomiting, chills and dizziness.</p> <p>Used WHO grading vs more</p>

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	<p>Amifostine works by selectively protecting normal but not tumor tissues from cytotoxic effects of RT and chemo</p>	<p>colorectal cancer & developed Grade 3 and 4 or persistent Grade 2 diarrhea (WHO) while undergoing adjuvant chemo with 5FU 500 mg/m² plus calcium folinate 50-100 mg/m² weekly.</p> <p>With Grade 2 or 3/4 diarrhea, chemo was first dose reduced by 10-20%.</p> <p>With Diarrhea Recurrence:</p> <ul style="list-style-type: none"> Group I (n=18): Continued treatment with initial dose of 5FU and calcium folinate plus amifostine 800 mg/m² weekly. Group II (n=16): Amifostine lowered to 500mg/m² weekly Group III (n= 18): dose of amifostine lowered to 150 mg/m²/ weekly <p>Amifostine toxicity defined as infusion-related hypotension.</p> <p>Primary endpoints: Proportion of 5FU/calcium folinate doses associated with diarrhea or amifostine toxicity.</p> <p>Secondary endpoints: Patient report of chemo-related adverse effects such as mucositis, anorexia, N & V and hematologic toxicity.</p>	<p>heme parameters were analyzed using dichotomous (binary) variables "decrease" or "increase".</p> <p>Paired comparisons used the McNemar test; independent comparisons used Pearson's chi-square ..</p>	<p>Incidence of diarrhea during baseline phase (all 52 pts) was the following:</p> <ul style="list-style-type: none"> WHO Degree 0= 9.9 % Degree 1: 52% Degree 2: 24.4 % Degree 3: 9.9 % Degree 4: 3.8 % <p>All pts received diphenoxylate or loperamide to control diarrhea; 12 also treated with octreotide until resolution of diarrhea; 7 readmitted for dehydration</p> <p>Compared with baseline, all doses of amifostine significantly reduced incidence of diarrhea (p<0.0001for each group) [Also beneficial in decreasing mucositis (p<0.04)]</p> <p>No differences between groups on severity of diarrhea</p> <p>Statistically significant difference in mean administered doses of 5-FU between pts prior to tx with amifostine (445 mg/m²) and subsequently (496-504 mg/m²); P<0.04</p> <p>No significant difference between mean 5-FU doses during tx with amifostine.</p> <p>Although previous studies found that doses of amifostine 740-910,....,are effective....., the current study suggests that lower doses may be effective and increase tolerability"</p> <p>High incidence of AEs (76.3% in</p>	<p>common NCI-CTC so will need to translate those results.</p> <p>Does not state the total dose of loperamide, etc that was used.</p> <p>No parallel non-treatment randomized control group so authors state the results should not be "regarded as definitive".</p>

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				<p>Group 1) though with complete resolution of Grade 3-4 or persistent Grad 1-2 5-FU related diarrhea.</p> <p>The primary adverse effect is hypotension and list: Baseline 0% Group 1 76% Group 2 54% Group 3 25%</p> <p>20% of usual dose of amifostine is capable of offering adequate protection against diarrhea and mucositis associated with 5FU.</p> <p>The 800 and 500 dose levels were equally effective to decrease the risk of all grades of diarrhea, but the lower dose was better tolerated. The 150 dose level was the best tolerated and was as effective as higher doses in preventing severe diarrhea and effective against prevention of grade 1 diarrhea, although slightly less effective than higher doses]</p> <p>Conclusions: Amifostine reduces the incidence and severity of diarrhea & mucositis associated with 5-FU & calcium folinate in patients with advanced CRC.</p> <p>Amifostine appears to offer protection against GI adverse effects and permit higher doses of 5-FU.</p>	
Neomycin for Prevention of Irinotecan-Related Diarrhea: ONS PEP Weight of Evidence Category: Benefits Balanced with Harms					
deJong et al, 2006	Patients were treated with Irinotecan 350mg/m2 during their first cycle combined with neomycin (n=28; 45%) or with	Double Blind Randomized Placebo-controlled study	NCI-CTC, version 2, used for diarrhea, nausea, and vomiting up to 3 wks following administration of irinotecan	Overall incidence and severity of delayed-type diarrhea did not differ significantly between study groups(p=.33)	Patients receiving neomycin had a 4.5 fold higher risk for grade 2 nausea than those receiving placebo (39.9% vs. 8.8%; p<.01).

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	<p>placebo (n=34;55%) Oral neomycin 660 mg 3 times daily was administered for 3 consecutive days starting 2 days before irinotecan.</p>	<p>The two groups well balanced for demographic parameters, hematological functions, bilirubin and liver enzyme values. The administered dose of Irinotecan did not differ significantly between groups(mean, 640 vs. 679mg,p=0.9)</p>	<p>Duration of diarrhea (in days) was scored</p>	<p>45% lower incidence of grade 3 diarrhea in group receiving neomycin vs placebo group (17.9%vs. 32.4%; p=.19) No difference between study group when grade 2&3 taken together (46.4% vs. 50.0%; p=.78)</p> <p>Tx with neomycin didn't result in a significantly shorter duration of diarrhea (4.0 vs. 4.9 days; p=.32)</p>	<p>Strength-study design</p> <p>Weakness-larger trial warranted</p>
Kehrer et al., 2000	<p>Patients experiencing equal to or greater than grade 2 diarrhea after receiving Irinotecan alone (350mg/m² q 3wks) then received the same dose combined with oral neomycin 1000mg tid continuously from 2 days prior to 5 days after the 2nd course</p> <p>This study was designed to evaluate irinotecan disposition and pharmacodynamics in the presence and absence of the broad-spectrum antibiotic neomycin</p>	<p>N = 20 patients with advanced CRC receiving CPT-11 (350mg/m² q 3wks)entered the study, 9pts developed grade 2 diarrhea in c#1 & received neomycin as co treatment in c#2. Non-randomized trial; patients acted as their own control</p>	<ul style="list-style-type: none"> • Presence of diarrhea (>4 stools per day) <p>Duration of diarrhea (measured in days)</p>	<p>No significant effect on hematological toxicity(p> 0.05) BUT diarrhea improved in 6/7 patients (p=0.033)</p> <p>Findings indicate that bacterial B-glucuronidase plays a crucial role in irinotecan induced diarrhea without affecting entero-cycling and systemic SN-38 levels</p>	<p>Weakness: extremely small study- this study was a pilot study to de Jong (2006)</p>
<p>Budesonide For Prevention of Irinotecan-Induced Diarrhea: ONS PEP Weight of Evidence Category: Effectiveness Not Established</p>					
Karthus et al, 2005	<p>Participants randomly assigned to</p> <ol style="list-style-type: none"> 1. 3mg budesonide po 3 times daily for a total of 8 weeks during 2 cycles of irinotecan 2. Placebo 	<p>Prospective, double-blind, placebo-controlled, multicenter, randomized Phase III randomized trial for prevention of diarrhea N=56 patients with advanced CRC receiving irinotecan (125 mg/m²) onc weekly</p>	<ul style="list-style-type: none"> • Presence of diarrhea (>4 stools per day) • Duration of diarrhea • Loperamide use <p>Measures recorded in patient diary</p> <p>Loperamide dose: 4 mg initially and then 2mg every two hours until diarrhea free for 12 hours</p>	<p>Superior prevention of diarrhea observed for budesonide compared to placebo (diarrhea could be prevented in 58.3% of the budesonide-treated patients compared to 38.5% of the placebo patients; p=0.257) Thus, although a trend exists, there is no statistically significant benefit in preventing irinotecan- induced diarrhea</p>	<p>Strength: study design (double-blind placebo-controlled design)</p> <p>Weakness: small study</p> <p>Lenfers (1999) noted efficacy of budesonide for patients failing loperamide. Therapeutic approach for inflamed bowel.</p> <p>Therapeutic administration might be more efficacious than prophylactic administration.</p>

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Charcoal For Prevention of Irinotecan-Induced Diarrhea: ONS PEP Weight of Evidence Category: Effectiveness Not Established					
Maeda et al, 2004	<p>Examination of effectiveness of 2 interventions to ameliorate diarrhea after treatment with irinotecan</p> <ol style="list-style-type: none"> Kremezin™ (AST-120) oral adsorbent made of activated carbon – 2 grams at start of irinotecan infusion, immediately after irinotecan, and 3 hrs later Oral alkalinization: 2 g NAHCO₃, 2g magnesium oxide, 300 mg ursodexychoic acid po before irinotecan, and then qd for 3 days after 	<p>Non-randomized trial. N = 13 Japanese patients with varying cancers receiving irinotecan (60 to 100 mg/m²) q 1-2 wks, alone or in combination regimen 7 patients: no prophylaxis (control) 4 patients: oral alkalinization (one was own control – received prior irinotecan with no prophylaxis) 4 patients: Kremezin™ (one was own control – received prior irinotecan with no prophylaxis)</p>	<p>Number of bowel movements Volume was not recorded</p>	<p>Oral Kremezin™ significantly decreased the maximum number of daily bowel movements during CPT-11 treatments as compared with no prophylaxis (p < 0.05)</p> <p>Oral alkalinization was effective in ameliorating diarrhea, although the efficiency did not reach a significant difference (no p value stated).</p>	<p>Small study with 13 patients total.</p> <p>One patient in Kremezin™ group and one in oral alkalinization group acted as their own control. Only 3 other patients were in each interventional treatment group.</p> <p>Although further study is necessary regarding the effect of oral Kremezin™ on plasma concentrations of irinotecan-related compounds, it is speculated that the absorption of irinotecan and/or SN-38 from the intestinal lumen is small, if any, and the remained irinotecan-related compounds in the intestinal lumen cause diffuse mucosal damage in irinotecan treatments.</p>
Michael et al, 2004	<p>Cycle 1 N=28 Patients received irinotecan plus oral activated charcoal (AC) 1000 mg plus 25 ml water the evening before irinotecan and then tid for 48 hours after on an empty stomach.</p> <p>Cycle 2 N=24</p>	<p>Prospective, non-randomized trial; patients served as their own control.</p> <p>Patients with advanced CRC receiving irinotecan 125 mg/m² weekly for 4 weeks with 2 weeks rest.</p>	<ul style="list-style-type: none"> NCI CTC diarrhea grade Loperamide consumption <p>Compliance with loperamide regimen – 4 mg at first onset of delayed diarrhea and then 2 mg every 2 hours (4 mg every 4 hours at night) until patient diarrhea free for 12 hours – was closely</p>	<p>Administration of AC with irinotecan in cycle #1 led to</p> <ul style="list-style-type: none"> Decreased grade 3 and 4 diarrhea Decreased loperamide consumption Increased irinotecan dose intensity 	<ul style="list-style-type: none"> Small sample size Patients acted as their own controls Complexities of irinotecan dose reductions and supportive care <p>Any statistical comparison in the efficacy parameters defined in the</p>

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	No AC		monitored by research nurses by inspection of a provided diary in which was recorded the daily loperamide consumption together with diarrhea frequency.	Grade 3-4 diarrhea 7.1% cycle 1 and 25% cycle 2. Grade 0 diarrhea 46.1% cycle 1 and 20.8% cycle 2. 98% planned dose delivered cycle 1; 70% cycle 2 25% took >10 loperamide cycle 1 and 54% in cycle 2.	trial would be associated with large CIs. An exploratory trial with small patient numbers; results are hypothesis generating and require additional confirmation in larger study.
Glutamine For Prevention Of Chemotherapy-Induced Diarrhea: PEP Weight of Evidence Category: Effectiveness Not Established					
Daniele et al., 2001	Randomized, double blind, placebo controlled, two armed, parallel trial	<p>Trial of 18 grams of glutamine vs placebo for 70 chemotherapy naive patients with colorectal cancer. Patients underwent chemotx with 5-Fluorouracil (FU) and folinic acid (FA).</p> <p>Glutamine or placebo was given for 15 consecutive days, beginning 5 days before chemotherapy. Patients received chemotherapy for a total of 5 days. The study was limited to the first cycle of chemotherapy.</p> <p>Note: Experimental dose (18 grams) is much greater than the normal dietary intake (1 gram).</p>	Measured intestinal absorption (IA) using d-xylose absorption test and intestinal permeability (IP) using cellobiose-mannitol permeability test. Both of these tests have been confirmed to be reliable and sensitive in clinical conditions characterized by disruption of the normal small intestinal mucosa (ex clinical conditions: celiac disease, Crohn's disease)	<p>For both placebo and control groups, chemotx induced worsening of IA and IP. When pre-treatment IA was compared to post-treatment IA, reduction in IA was significantly greater in the placebo group (p=0.02).</p> <p>Higher incidence of diarrhea in the placebo group, though not statistically significant (p=0.09).</p> <p>Significant difference in use/need for loperamide (i.e. placebo group had higher mean number of loperamide tablets; p=0.002). No difference in episodes of nausea, vomiting, haematological toxicity</p> <p>Overall conclusion: glutamine reduces changes in IA and IP during chemotherapy with FU and may have a protective effect against diarrhea by enhancing the barrier function of the intestine.</p>	<p>LIMITATIONS Sample size needed for statistical analysis =70, only 62 patients included in final analysis</p> <p>Analysis specific to chemotx using 5-Fluorouracil and folinic acid only.</p> <p>STRENGTHS Used sensitive and reliable tests evaluating the morphological changes to the intestine that are casually related to incidence of diarrhea.</p> <p>Results are consistent with previous studies suggesting that there are protective effects of glutamine on the intestinal mucosa</p>
Glutamine For Prevention Of Radiation-Induced Diarrhea: PEP Weight of Evidence Category: Effectiveness Not Established					
Kozelsky et al., 2003	Patients were stratified by the following: history of anterior resection of the rectum vs no prior rectal surgery; total	Two-arm, placebo-controlled, randomized clinical trial. N=129 patients from 14 institutions.	Primary measure of treatment efficacy was diarrhea levels measured during evaluation by radiation oncology RN and via	No significant difference in incidence of diarrhea (p=0.99); no significant difference in stools per day, maximum stools per day,	LIMITATIONS Inconsistent with other studies which found significant effect (improvement) in diarrhea with

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	planned cumulative radiation dose, use of FU and primary tumor site (rectal vs prostate vs gynecological vs other.) After stratification, patients were randomly assigned to experimental group (4 grams of glutamine BID for 7 days a wk during radiation and for 2 wks thereafter) or identical appearing placebo (glycine) for the same time period.	Study design was based on goal of 120 patients, so that two-sided 0.05 level Wilcoxon rank sum would have a power of 97.5% to detect an improvement in diarrhea severity.	bowel function questionnaire. Questionnaire was derived from previous studies on radiation therapy and bowel fxn. Participants completed questionnaire weekly for 4 weeks, then at 12 and 24 month follow up. Toxicity was measured using NCI diarrhea toxicity criteria.	antidiarrheal agent used, use of loperamide	glutamine supplementation. Further research needed to determine whether lower dose of glutamine was used in this study (vs Daniele et al) Authors did not report on the validity/reliability of bowel fxn questionnaire. No dose-response data to assess whether higher dose of glutamine and/or longer use of glutamine pre-treatment would have been more effective in treating/preventing diarrhea.
Oral Alkalinization For Prevention of Irinotecan-Induced Diarrhea: ONS PEP Weight of Evidence Category: Effectiveness Not Established					
Maeda et al, 2004	Examination of effectiveness of 2 interventions to ameliorate diarrhea after treatment with irinotecan 1. Kremezin™ (AST-120) oral adsorbent made of activated carbon – 2 grams at start of irinotecan infusion, immediately after irinotecan, and 3 hrs later 2. Oral alkalinization: 2 g NaHCO ₃ , 2g magnesium oxide, 300 mg ursodexychoic acid po before irinotecan, and then qd for 3 days after	Non-randomized trial. N = 13 Japanese patients with varying cancers receiving irinotecan (60 to 100 mg/m ²) q 1-2 wks, alone or in combination regimen 7 patients: no prophylaxis (control) 4 patients: oral alkalinization (one was own control – received prior irinotecan with no prophylaxis) 4 patients: Kremezin™ (one was own control – received prior irinotecan with no prophylaxis)	Number of bowel movements Volume was not recorded	Oral alkalinization was effective in ameliorating diarrhea, although the efficiency did not reach a significant difference (level of significance not indicated). Oral Kremezin™ significantly decreased the maximum number of daily bowel movements during irinotecan treatments as compared with no prophylaxis (p<0.05)	Small study with 13 patients total. One patient in Kremezin™ group and one in oral alkalinization group acted as their own control. Only 3 other patients were in each interventional treatment group.
Moreno et al, 2006	N=24 patients with gastrointestinal carcinoma receiving varying irinotecan-based regimens from 4 Spanish community practice settings	Experimental interventional prospective study. No control	Diarrhea grade, although no mention of which grading scale was used.	4 of 24 (16%) of patients had grade III-IV diarrhea (8 had prior pelvic RT, a risk factor associated with diarrhea) Comparison was made to incidence of grade II-IV diarrhea in	<ul style="list-style-type: none"> Uncontrolled trial Small numbers

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	2 g of powdered NaHCO ₃ diluted in 250 ml water was sipped during the days of irinotecan administration starting in the morning. Other fluids were taken ad lib.			previous colorectal cancer studies. Researchers' conclusion: intestinal alkalization may be effective in preventing diarrhea with patients with gastrointestinal cancer receiving irinotecan.	
Takeda, 2001	<p>Oral alkalization (OA) combined with control of defecation (CD)</p> <p>OA: 0.5 g NaHCO₃ and 0.5 g Magnesium oxide pc and hs, basic water (ph>7.2) continuously for total of 1500-2000 mL/d and ursodeoxycholic acid 100 mg po pc d 1-4</p> <p>CD: (administering laxative treatment to avoid long contact time of irinotecan metabolite with bowel mucosa): doses of up to 4g/day of Magnesium oxide and 2L/day of excess basic water served purpose of CD</p> <p>If watery diarrhea with OA and CD, magnesium oxide discontinued until symptom resolution</p>	<p>Case control study with Japanese SCLC or NSCLC patients from a single institution</p> <p>Group B: 37 consecutive patients from 3 ongoing prospective phase I/II studies receiving irinotecan in combination with Cisplatin in the presence of OA and CD</p> <p>Group A: 32 control subjects matched to the background characteristics of the case patients treated with irinotecan and Cisplatin without OA and CD</p>	<p>Intraluminal pH</p> <p>Hematologic toxicity</p> <p>Non-hematologic toxicity</p> <ul style="list-style-type: none"> GI (Appetite loss, N/V, Constipation, Delayed diarrhea, amount of loperamide used) Dose intensity and response <p>How loperamide use was measured, was not mentioned in article. Loperamide dose: 2mg on demand after every diarrheal episode. When this approach did not succeed, the patient was managed with 2mg of loperamide every 4 hours routinely until diarrhea free for 12 hours.</p>	<p>ECOG CTC</p> <p>OA and CD resulted in</p> <ul style="list-style-type: none"> Higher stool pH (p<0.0001) Reduced incidence delayed diarrhea ≥ grade 2 (group A 32.3% vs group B 9.4% p=0.005) Duration delayed diarrhea group A 2.8 times longer than B (p<0.0001) Loperamide use greater group A (p=0.003) Nausea (p=0.0001) Vomiting (p=0.001) Myelotoxicity (p=0.03) Lymphocytopenia (p=0.034) Dose intensification with OA and CD (from 34.6 to 39.9 mg/m²/wk (p<0.001) Tumor response rates Group B 59.3% vs Group A 38.5% (p=0.173) 	<p>Pt. response rates did not indicate that OA and CD compromised clinical efficacy of irinotecan and Cisplatin therapy. Although a reduced amount of irinotecan and SN-38 may be circulated enterohepatically, the increased dose intensity conferred by OA and CD results in maintenance of same degree of clinical efficacy.</p> <p>OA and CD appear useful in preventing dose-limiting side effects of irinotecan, mainly nausea, vomiting, granulocytopenia, delayed diarrhea</p>
Flieger et al., 2007	Each patient took levofloxacin 500 mg tablets once at 8 pm and cholestyramine 4 g tid, not together with other medications. from day -1 to day +1 of administration of irinotecan 250 mg/m ² IV over 90 minutes every two weeks, For treatment of acute cholinergic syndrome, of	<p>Phase II trial</p> <p>N = 51 patients with metastatic CRC in second-line treatment</p> <p>No prior therapy with irinotecan; refractory or resistant to 5-FU</p>	<p>Prevention of delayed diarrhea</p> <p>Self-report patient diary completed following each dose of chemotherapy</p> <p>WHO grading of diarrhea</p>	<p>Combination of cholestyramine/levofloxacin is a promising option for prevention of delayed diarrhea caused by irinotecan and may help to escalate the dose of irinotecan in the future.</p> <p>Incidence of 2% of WHO grade 3 diarrhea ; no grade 4; 225 had WHO grades 1-4 diarrhea</p>	<p>Weaknesses:</p> <ul style="list-style-type: none"> Small study Phase II study No pharmacokinetic analyses of the active metabolite SN-38 and SN-38G in plasma <p>No info on effect of cholestyramine affects to irinotecan efficacy (if</p>

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	abdominal cramping and early diarrhea, atropine 0.25-1 mg IV was administered. For treatment of delayed diarrhea, loperamide was offered if necessary.			Compared with reported incidence in the order of up to 40% in the literature without prophylaxis 78% had no diarrhea; 20% had grades 1 and 2	decreases effects, could decrease incidence of diarrhea)
<p>Probiotics For Prevention Of Chemotherapy-Induced Diarrhea: PEP Weight of Evidence Category: Effectiveness Not Established</p>					
Bowen et al, 2007	Animal study: VSL #3 (probiotic) was administered to female rats being treated with Irinotecan.	<p>N=48 female rats Rats were randomly divided into 8 groups of 6 rats, as follows: 1)untreated controls 2)Irinotecan only 3)Irinotecan + probiotic for 21 days prior to treatment 4)Irinotecan + probiotic (28 days combined pre and post-treatment) 5)Irinotecan + probiotic (7 days post treatment) 6)Probiotic only (21 days) 7)probiotic only (28 days) 8) probiotic only (7 days)</p> <p>Rats were treated with irinotecan due to the proven side effect of diarrhea with irinotecan treatment.</p>	<p>All animals were assessed four times daily after administration of irinotecan. Assessments included: 1) change in temperament 2) presence of diarrhea 3) weight loss 4) reluctance to move</p> <p>Intestines were collected at study completion to study histological and proliferative changes, as well as apoptosis levels and mucin composition.</p>	<p>1) Response to treatment: mortality was not associated with effects of probiotic on the gut 2) Diarrhea: 50% of the rats treated with irinotecan developed severe diarrhea and 17% developed moderate diarrhea. Rats treated with VSL#3 before and after irinotecan did not develop moderate or severe diarrhea. 3) Organ weights: There was a significant increase in small intestinal weight in all groups treated with irinotecan compared to controls (p<0.001). There was no difference in small intestinal weight between groups treated with VSL#3. There was also a significant increase in large intestinal weight among rats treated with VSL#3 either before irinotecan or after irinotecan only (p<0.001 and p<0.05 respectively) when compared to controls.</p> <p>The authors conclude treatment with VSL#3 before and after irinotecan chemotherapy reduced weight loss and prevented moderate and severe diarrhea. The authors state that the conclusions are associated with histological changes in the small and large intestines. As a result, the authors suggest that VSL #3 is</p>	<p>LIMITATIONS Animal study, therefore results may not be applicable to human population.</p> <p>STRENGTHS Controlled for effect of probiotic, as well as duration and timing of probiotic dose</p> <p>Assesses histological changes in the intestinal tract to support etiology of diarrhea.</p>

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				effective at preventing severe diarrhea following chemotherapy with irinotecan, and has the potential to be used for the prevention of diarrhea among cancer patients.	
Osterlund et al., 2007	<p>Open-label, prospective, randomized, phase III, single institution, 2x3 factorial design study of patients receiving adjuvant chemotherapy after surgery.</p> <p>Variables of the study included the following:</p> <p>1. <u>Chemotherapy regimen:</u> patients were randomized at a 1:1 ratio to either the Mayo regimen or simplified de Gramont regimen, as described below:</p> <p>a. Mayo regimen: short IV infusion of leucovorin (LV) and 5-FU over 3-5 minutes on days 1-5 of cycle with four week intervals x six intervals (total chemotherapy time = 24 weeks) versus</p> <p>b. simplified de Gramont regimen: 2 hour infusion of LV followed by 5-FU bolus and then 48 hour infusion of 5-FU every 14 days for 12 times (total chemotherapy time = 24 weeks)</p> <p>2. <u>Probiotic supplementation:</u> Patients were randomized at a 2:1 ratio to receive <i>Lactobacillus rhamnosus</i> GG (ATCC 53103) at a dose of 1-2X10¹⁰ per day for 24 weeks of chemotherapy (i.e., 98 patients received <i>Lactobacillus</i>, 52</p>	<p>N = 148 patients aged 18-75 years (median age 60 years) with histologically confirmed colorectal cancer that had been removed via surgery; no metastases found on US or CT of the abdomen, chest x-ray, or CT of the thorax;</p> <p>All patients received chemotherapy. A subset of patients (n = 39) also received radiation therapy</p> <p>Treatment-related side effects were recorded in a diary kept by the patients and by a physician and evaluated during each treatment cycle.</p> <p>Data collected on 148 of the subjects with 97 in treatment group and 51 not receiving treatment.</p>	<p>Primary endpoint was frequency of severe diarrhea, as defined by the Common Toxicity Criteria of the National Cancer Institute of Canada Scale</p>	<p><u>Chemotherapy regimen:</u> The de Gramont regimen was better tolerated than the Mayo regimen</p> <p><u>Probiotic supplementation:</u></p> <ol style="list-style-type: none"> 1. Patients who received <i>Lactobacillus rhamnosus</i> GG supplements had significantly less grade 3 or 4 diarrhea (p = 0.027), 2. Patients receiving LGG supplements had significantly less abdominal discomfort from flatulence, borborygmia, or abdominal distention (p = .025) 3. LGG had no significant effect on the overall toxicity of treatment, frequency of stomatitis or neutropenia 4. None of the patients had LGG growth in blood bacterial cultures <p><u>Guar gum supplementation:</u> Guar gum supplementation (11 g) had no effect on the following:</p> <ol style="list-style-type: none"> a. chemotherapy toxicity (i.e., diarrhea) p = 0.13 b. the frequency of severe diarrhea (p = 0.24) c. abdominal discomfort from flatulence, 	<p><u>Limitations:</u> Chemotherapy regimen did not contain commonly used chemotherapy agents for colorectal cancer (i.e., irinotecan, capecitabine, or oxaliplatin)</p> <p>Study was not placebo-controlled, nor was the study blinded to administration of dietary supplements.</p> <p><u>Study flaws:</u> Metoclopramide and 5HT₃ inhibitors were used to treat nausea and vomiting; metoclopramide may influence diarrhea due to its influence on peristalsis/gastric emptying</p> <p>Multiple interventions (treatment regimen, use of probiotics, and use of fiber supplement), therefore difficult to control all variables and/or to identify causal factors</p> <p>Guar gum supplement also high in kcal/protein, therefore additional ingredients may influence diarrhea episodes (i.e., not isolated fiber supplement only)</p> <p>Note: Authors are planning a prospective, randomized, multicenter, double-blind, placebo-controlled study with a cross-over design to assess effects of</p>

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	<p>patients did not)</p> <p>3. <u>Fiber supplementation:</u> Patients were randomized at a 1:2 ratio to receive Guar Gum supplementation of 500 ml, 11 g guar gum in 550 kcal and 20 g protein on cycle days 7-14 for eight days per month</p> <p>All patients received dietary counseling; no other diet supplements were allowed during study</p>			<p>borborygmia, or abdominal distention (p = 0.20)</p> <p><u>Combination of <i>Lactobacillus</i> and guar gum fiber</u> One-third of the patients received both lactobacilli and guar gum. No further reduction in gastrointestinal adverse effects was detected (beyond reduction from lactobacillus supplements alone)</p> <p><u>Overall conclusions:</u> Daily oral administration of <i>Lactobacillus rhamnosus</i> GG may reduce the frequency of severe 5-FU-based chemotherapy-induced diarrhea. Further studies are needed.</p>	<p><i>Lactobacillus</i> supplementation during chemotherapy with capecitabine, oxaliplatin, irinotecan and bevacizumab.</p>
<p>Vitamins E and C for Treatment of Radiation-Induced Diarrhea: ONS PEP Weight of Evidence Category: Effectiveness Not Established</p>					
<p>Kennedy, 2001</p>	<p>Aim of the study was to determine whether antioxidant vitamins, by counteracting oxygen free radical injury would relieve symptoms of chronic radiation proctitis. Patients received 400 IU vitamin E and 500 mg vitamin C tid for 8 weeks. Patients were experiencing persistent, post-radiation proctitis with disabling diarrhea, urgency or fecal incontinence.</p>	<p>Non-randomized, before and after design (patients were their own controls) 20 consecutive patients from a single gastroenterology clinic</p> <p>10 prostate cancer survivors 10 gynecologic cancer survivors</p>	<p>Questionnaire: Severity, Frequency and Life-style impact each rated as (0-4) Rectal bleeding Rectal pain Diarrhea Fecal urgency</p>	<p>14 of 16 patients reported less diarrhea and 8 said diarrhea stopped completely. Among patients with rectal bleeding or urgency, symptoms completely resolved in 36% and 19% respectively. Lifestyle improved in 13 patients and 7 reported return to normal.</p>	<p>Non-randomized and non-controlled study from a single clinic with a small sample size. Intervention represents low risk of harm.</p>
<p>Pentosan Polysulfate (PPS) for Treatment of Radiation-Related Diarrhea: ONS PEP Weight of Evidence Category: Effectiveness Unlikely</p>					
<p>Pilepich, 2006</p>	<p>Note: PPS is a glycosaminoglycan marketed as Elmiron and Benechemie which has been used to treat radiation-induced sequelae of the bladder.</p>	<p>180 patients from 34 institutions, 168 evaluable</p> <p>300 mg/day n=48 600 mg/day n=50 Placebo n=53</p>	<p>NCI Toxicity Criteria (0-4) for Proctitis, diarrhea, Melena</p> <p>Complete Response = Absence of symptoms and cessation of symptom medications</p>	<p>No significant difference was found among the three arms of the study.</p>	<p>Previous pilot study had more promising results not replicated in this study. Recommendations are for further dosing trials or possible rectal administration.</p> <p>20-25% of the subjects were</p>

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	Patients were randomized to one of 3 arms: 100 mg PPS tid, 200 mg PPS tid, or placebo tid. If no improvement in 2 months treatment was d/c. If symptoms improved or resolved, treatment was continued for an additional 4 months.	Subjects had received RT to the abdomen or pelvis and experienced treatment-related proctitis, diarrhea, and melena at least 4 wks after completion of therapy (grade 1-3 toxicity by NCI criteria) No concurrent chemo included	Partial Response = Reduction in severity grade QOL endpoints: FACE FACT SF-12 SQLI		reported to have deteriorated in the first 3 months of the study.
Sucralfate for Prevention of Radiation-Related Diarrhea: ONS PEP Weight of Evidence Category: Not Recommended for Practice					
Martenson, 2000	Pts receiving pelvic XRT were randomly assigned to receive sulcralfate (2 GM qid) vs placebo (double blind)	123 evaluable patients 62 in treatment group and 61 in placebo, with balance between groups in terms of diagnosis, functional status, radiation dosage, tumor status etc. Randomized, double-blind controlled trial	Weekly Patient Questionnaire of Reported Symptoms (cramping, # bowel movements, blood, nocturnal BMS, fecal incontinence, use of protective clothing) Physician-reported toxicity grading diarrhea, tenesmus, cramping, bleeding, nausea and constipation (none, mild, moderate, severe) from NCI criteria.	Sulcralfate did not decrease pelvic RT-related bowel toxicity by any of the end points measured and seems to have aggravated some gastrointestinal symptoms. More patients in the treatment group(34% vs 16% in the placebo group) reported fecal incontinence and a need for more protective clothing (P=.04) and physician-reported severity of nausea was worse in the treatment group (P=0.3) – although this was not a specific study endpoint.	Of concern is the physician reported toxicity ratings and how the ratings were derived – the patient questionnaire does approximate the physician scale so the information would be collected directly from the patient, but provider assessments of subjective data (like cramping, straining etc) can be unreliable if not obtained directly from the subject.