

Endoscopic and non-endoscopic approaches for the management of radiation-induced rectal bleeding

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Author contributions: Weiner JP and Schreiber D equally contributed to this paper with conception and design of the review article, literature review and analysis, drafting and critical revision and editing, and final approval of the final version; Wong AT, Schwartz D, Martinez M and Aytaman A contributed to the critical revision and editing and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest, no financial support.

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Manuscript source: Invited manuscript

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Received: March 29, 2016
Peer-review started: April 4, 2016
First decision: May 30, 2016
Revised: June 12, 2016
Accepted: July 6, 2016
Article in press: July 6, 2016
Published online: August 21, 2016

Abstract

Pelvic radiation is a commonly utilized treatment for malignancy of the genitourinary and lower gastrointestinal tract. Radiation proctitis and the resultant clinical picture varies from asymptomatic to potentially life threatening. Similarly, treatment options also vary greatly, from medical therapy to surgical intervention. Commonly utilized medical therapy includes sucralfate enemas, antibiotics, 5-aminosalicylic acid derivatives, probiotics, antioxidants, short-chain fatty acids, formalin instillation and fractionated hyperbaric oxygen. More invasive treatments include endoscopic-based, focally ablative interventions such as dilation, heater and bipolar cautery, neodymium/yttrium aluminum garnet argon laser, radiofrequency ablation or argon plasma coagulation. Despite its relatively common frequency, there is a dearth of existing literature reporting head-to-head comparisons of the various treatment options *via* a randomized controlled approach. The purpose of our review was to present the reader a consolidation of the existing evidence-based literature with the goal of highlighting the comparative effectiveness and risks of the various treatment approaches. Finally, we outline a pragmatic approach to the treatment of radiation proctitis. In light of the lack of randomized data, our goal is to pursue as least invasive an approach as possible, with escalation of care tailored to the severity of the patient's symptoms. For those cases that are clinically

asymptomatic or only mildly symptomatic, observation or medical management can be considered. Once a patient fails such management or symptoms become more severe, invasive procedures such as endoscopically based focal ablation or surgical intervention can be considered. Although not all recommendations are supported by level I evidence, reported case series and single-institutional studies in the literature suggest that successful treatment with cessation of symptoms can be obtained in the majority of cases.

Key words: Prostate cancer; Radiation therapy; Radiation proctitis; Radiation proctopathy; Medical treatment; Endoscopic treatment; Hyperbaric oxygen; Neodymium/yttrium aluminum garnet argon laser; Argon plasma coagulation

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Core tip: Rectal bleeding due to radiation proctitis is a relatively common and potentially devastating consequence of modern radiation therapy. Possible treatment options for radiation proctitis include observation, medical therapy, endoscopic-based therapy and surgery. There is a lack of data from randomized controlled trials to help inform the clinician's decision making process with respect to treatment. Our objective is to consolidate current literature to better inform the reader of potential risks, benefits and outcomes of such treatment approaches as well as present a practical approach for the management of radiation proctitis.

Weiner JP, Wong AT, Schwartz D, Martinez M, Aytaman A, Schreiber D. Endoscopic and non-endoscopic approaches for the management of radiation-induced rectal bleeding. *World J Gastroenterol* 2016; 22(31): 6972-6986 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i31/6972.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i31.6972>

INTRODUCTION

Neoplasms of the genitourinary and lower gastrointestinal tract are among the most frequently diagnosed cancers in the United States^[1]. It is estimated that almost 400000 patients will be diagnosed in 2016 with either prostate, urinary bladder, uterus, rectum, cervix or anal cancer^[1]. The utilization of radiation therapy to these sites, as either definitive monotherapy or as part of a multi-modality treatment approach, is delivered in an estimated 30%-60% of these patients^[2,3]. Thus, a great number of patients are exposed to pelvic radiation every year. A possible consequence of radiation therapy to an intended target organ is the unwanted exposure to adjacent healthy tissues, particularly the rectum or sigmoid colon. Patients receiving pelvic radiation will often experience an acute temporary worsening of rectal symptoms

with a return to baseline by 6 mo after therapy^[4,5]. Radiation dose to the rectum can less often result in the development of late complications such as radiation proctitis, which is broadly defined as epithelial damage to the colon due to radiation treatment^[6].

Most series in the literature suggest an incidence around 5% for chronic radiation proctitis after pelvic radiation^[7]. Although, some studies suggest the incidence could be as high as 20%-30%, due to a vast underdiagnoses of this condition^[8]. As such, the true epidemiology of radiation proctitis is difficult to characterize given the variety of cancer sites and radiation treatment schemes. Given the relative frequency of incidence, clinicians are likely familiar with the most frequent constellation of symptoms seen with radiation proctitis: diarrhea, urgency, rectal bleeding and/or fecal incontinence^[9].

Like all deterministic radiation effects, radiation proctitis has an apparent threshold dose and the severity of the consequence depends of the amount of absorbed dose^[10]. Doses of radiation less than 45 Gy are seldom associated with long-term side effects to the rectum, while doses above 70 Gy have been noted to cause significant injury^[11]. Doses between 45 and 70 Gy have a more variable association with radiation proctitis, as the likelihood of developing injury is related to both patient factors, such as smoking, diabetes, vascular disease or inflammatory bowel disease^[12,13], and treatment factors, such as total radiation dose, dose per fraction, technique, and treatment volume^[14].

CLASSIFICATION AND DIAGNOSIS

Essential to the diagnosis and management of any treatment-related complication is a system of classification. This allows for a more objective approach to the stratification of observed toxicity and helps physicians make an informed management decision. Most reported literature describes radiation-related gastrointestinal toxicity using the Radiation Therapy Oncology Group (RTOG) scoring criteria^[15]. A user-friendly modified version is shown in Table 1^[16].

When a diagnosis of radiation proctitis is suspected due to the presence of associated symptoms and prior treatment with radiation therapy, a thorough history including risk factors for other causes of colitis should be elicited. Such factors include recent use of medications like antibiotics, which may induce overgrowth of *Clostridium difficile*, or overuse of nonsteroidal anti-inflammatory drugs (NSAIDs) which can mimic symptoms of radiation proctitis. Travel history should also be obtained with emphasis on recent travel to an area with endemic parasitic infections such as amebiasis or giardiasis. A sexual history should be obtained for risk factors of certain sexually transmitted infections, such as *Neisseria gonorrhoea* and herpes simplex virus, as these have been associated with proctitis. Finally, it is important

Table 1 Modified radiation therapy oncology group rectal toxicity scale

	Clinical summary	Symptom and intervention
Grade 0	No impact	No discernable symptoms or intervention
Grade 1	Mild and self-limiting	Minimal, infrequent bleeding or clear mucus discharge, rectal discomfort not requiring analgesics, loose stools not requiring medications
Grade 2	Managed conservatively, lifestyle (performance status) not affected	Intermittent rectal bleeding not requiring regular use of pads, erythema of rectal lining on proctoscopy, diarrhea requiring medications
Grade 3	Severe, alters patient lifestyle	Rectal bleeding requiring regular use of pads and minor surgical intervention, rectal pain requiring narcotics, rectal ulceration
Grade 4	Life threatening and disabling	Bowel obstruction, fistula formation, bleeding requiring hospitalization, surgical intervention required
Grade 5	Death	Death directly related to radiation effects

Table 2 Comparison of acute vs chronic radiation proctitis

	Acute proctitis	Chronic proctitis
Symptom development	≤ 3 mo from start of radiation	> 3 mo from start of radiation to years later
Incidence	Common (50%-100%)	Less common (2%-20%)
Common symptoms	Diarrhea, urgency, pain	Rectal bleeding
Rare symptoms	Significant rectal bleeding	Stricture, obstruction, fistula
Histopathology	Epithelial cell depletion with inflammatory infiltrate	Small vessel changes without inflammatory infiltrate
Treatment	Conservative, medical	Conservative, medical, endoscopic, surgical

to note that a history of radiation treatment outside of the suspected area of proctitis (*i.e.*, brain radiation with rectal bleeding) should NOT warrant suspicion for radiation proctitis, as areas outside of the radiation portal only receive a scattered dose of < 1% of the total prescribed dose^[17].

Formal diagnosis of radiation proctitis does necessitate direct visualization of the suspicious post-irradiated tissues. Mucosal features indicative of radiation proctitis include pallor, friability and telangiectasias^[18]. Biopsy of the area is not necessary, though this can help rule out other causes for symptoms on the differential diagnosis, like inflammatory bowel disease or malignancy. The decision to biopsy any site with prior high-dose radiation should not be made lightly and should be a collaborative effort between the Endoscopist and the Radiation Oncologist, as biopsy has been linked to the development of fistulae^[19].

ACUTE VS CHRONIC RADIATION PROCTITIS

The diagnosis of radiation proctitis can be separated into two distinct categories, acute or chronic, based

on the timing to the development of symptoms with respect to delivery of radiation therapy^[20]. These two groups have different presenting symptoms, incidence, histopathological findings, and treatment approaches which are summarized in Table 2. Symptoms that develop within 3 mo from the initiation of radiation are classified as acute while those developing after are chronic. Brisk acute injury can persist into a consequential late effect, or late proctitis can develop in the absence of acute proctitis after a latent period of months to years after initial exposure^[10].

The clinical picture of radiation proctitis varies from asymptomatic to potentially life threatening. Acute proctitis presents more commonly with diarrhea, urgency or abdominal/pelvic pain, while bleeding and fecal incontinence occur less commonly^[21]. Chronic radiation proctitis can include any of the acute symptoms that persist past three months after the initiation of treatment or develop independently at a later time. In addition, it presents more frequently with rectal bleeding as a symptom compared to acute proctitis. Finally, chronic radiation proctitis can also include the development of symptoms that generally not seen in acute proctitis, such as stricture, obstruction or fistula formation^[22].

The reported incidence of any transient acute radiation proctitis is thought to range from 50% to 100%^[23], while the incidence of chronic proctitis is considerably less common with estimates ranging from 2% to 20% of all patients treated with radiation for pelvic malignancy^[21]. The median time for the development of chronic symptoms after radiation treatment is between 8 to 13 mo in the majority of series^[24,25]. Although, a few series do report a considerably longer latent period, with initial symptoms developing more than 30 years after completing radiation^[26].

While acute radiation proctitis is characterized by superficial epithelial cell depletion with acute inflammatory infiltrate in the lamina propria^[27], the

causative histopathological finding associated with chronic radiation proctitis are due to small vessel vasculopathy leading to secondary changes such as submucosal fibrosis, obliterative endarteritis and the presence of fibrin thrombi with resultant increased vascular resistance^[28]. A key distinction between acute and late proctitis is the relative lack of inflammatory infiltrate in the latter.

PREVENTION

Modern oncologic care has progressed to such a degree that there is an increasing weight given not only to the efficacy of treatment and associated outcomes, but on the safety and morbidity of treatment as well. Unwanted radiation injury to the lower gastrointestinal tract can be minimized by two general principles: reducing the dose delivered to normal structures or reducing the radio-sensitivity of the organ at risk.

Reducing the radiation dose to the organs at risk has historically been achieved through physical means. Though simple, changing the physical measures of patient setup, such as supine vs prone placement or daily treatment with a full bladder vs an empty bladder, has been shown to have an impact on dosimetric and clinical outcomes^[29]. A study reported by Bayley *et al*^[30] showed that for patient's treated for prostate cancer, the supine patient position decreased dose to rectal wall compared to the prone position. More invasive techniques of physically displacing organs at risk have been developed. For men with prostate cancer, a 50% dose reduction to the rectal wall has been achieved through a quick, outpatient trans-perineal injection of a collagen spacer^[31]. This spacer increased the distance between the rectal wall and the prostate gland, thus allowing additional dose fall off and sparing of the rectum.

However, the movement of dose away from organs at risk can also be accomplished through technological advances in radiation delivery. Over two decades ago conventional radiation therapy, in which target delineation was based on bony anatomy *via* orthogonal films, was superseded by three-dimensional conformal radiotherapy (3DCRT), which bases treatment planning off of computed tomography (CT) images. The use of CT-based planning has been shown to decrease the volume of unintentionally irradiated bowel compared to conventional radiotherapy^[32]. Another addition that 3DCRT has introduced is the "dose-volume histogram" (DVH), which is a graphical display of the dose distribution within a volume of interest^[33]. The DVH has allowed Oncologists to now generate information about specific dosimetric parameters with respect to organ tolerance and represents a cornerstone of modern radiotherapy quality assurance.

More recently, the last decade has seen increasingly complex methods of treatment delivery including intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT) and volumetric-

modulated arc therapy (VMAT). These techniques use a combination of inverse planning with multiple beams of varying intensity, real-time organ motion management and/or treatment with a rotating gantry to deliver the most advanced external beam planning to date^[34,35]. Some have argued that these increasingly sophisticated techniques should eventually prevent patients from developing adverse effects like radiation proctitis. Indeed, numerous reports in the literature do support a decrease in the observed number of gastrointestinal side effects when using advanced techniques in several pelvic sites including prostate, cervix, endometrium and anal cancer^[36-40]. Despite these advances in preventing radiation proctitis, our current technology has been unable to reduce the number of patients experiencing side effects to zero^[41].

The second strategy to prevent radiation-induced injury to the gastrointestinal tract is to utilize biological approaches to modulate the relative radiosensitivity or resistance of normal tissue to ionizing radiation. Two broad categories of such approaches can be broken down *via* the timing of administration. If given prior to delivery of radiation, they are categorized as radioprotectors; if administered during a course of radiation they are categorized as radiomitigators. Though not widely adopted, such agents include biological, chemical and pharmacological interventions. Due to numerous reasons, including fears over protection of malignant cells in addition to healthy cells, there is a lack of clinical evidence for these agents besides small, usually single center reports.

The one exception to this rule remains amifostine, which is a potent scavenger of reactive oxygen species. Prior investigation has shown that amifostine is able to exert protective effects due to reducing injury *via* free radicals on intestinal cells^[42]. A randomized trial reported by Athanassiou *et al*^[42] showed that daily intravenous use of amifostine prior to daily radiation decreased the development of radiation proctitis during pelvic irradiation without evidence of tumor protection. An additional randomized trial by Liu *et al*^[43] came to the same conclusion *via* treatment with daily intravenous amifostine. A more recent study from authors at the National Institute of Health assessed the effect of two different dose levels of intrarectal amifostine on quality of life and bowel function for men with localized prostate cancer undergoing radiation^[44]. The larger dose of amifostine was noted to produce significant improvement in acute and late bowel quality of life. Despite this data from several randomized trials, the routine adoption of amifostine for the prevention of radiation proctitis remains limited. This is likely due to the toxicities associated with amifostine, particularly severe hypotension, which limit the therapeutic ratio derived from its use.

TREATMENT APPROACHES

Treatment options for radiation proctitis vary from

Table 3 Non-endoscopic medical therapy for radiation proctitis

	Proposed mechanism	Indications
Sucralfate	Protection from injury	RCT supports treatment of chronic proctitis
Metronidazole	Antibiotic/ Immunomodulator	RCT supports treatment of chronic proctitis
5-aminosalicylic acid derivatives	Anti-inflammatory	Mixed results
Probiotics/ antioxidants	Immunomodulator/ free radical scavenger	Mixed results, but with minimal side effects
Butyrate	Colonocyte nutrient	RCT supports treatment of acute proctitis
Topical formalin	Coagulative necrosis	Effective for chronic proctitis though significant morbidity
Hyperbaric oxygen	Promotes angiogenesis and healing	RCT supports treatment of chronic proctitis

RCT: Randomized controlled trial.

conservative approaches such as observation and medical management, to invasive endoscopic or surgical intervention^[45]. Commonly utilized medical therapy includes sucralfate enemas, antibiotics, 5-aminosalicylic acid derivatives, probiotics, antioxidants, short-chain fatty acids, formalin instillation and fractionated hyperbaric oxygen. More invasive treatments include focally ablative endoscopically-based interventions such as dilation, bipolar cautery, neodymium/yttrium aluminum garnet argon (Nd:YAG)/potassium titanyl phosphate (KTP) laser, radiofrequency ablation or argon plasma coagulation. Even surgical therapies such as diverting ostomy, reconstruction, proctectomy or pelvic exenteration have been employed as a treatment option. Despite its relative frequency, the optimal intervention for radiation proctitis has yet to be defined, as there is a lack of large randomized controlled trials examining the comparative effectiveness of various treatment options^[46]. Treatment algorithms incorporating many of these aforementioned interventions have been previously proposed and shown to be efficacious in improving patient-reported quality of life^[47].

Therefore, patient management is informed mainly as a consequence of case reports or small, single-armed clinical trials. A periodic review and update of existing literature is thus a way to compile evidence to assist decision-making. Though reviews on the topic of radiation proctitis have been previously reported in the literature, few account for both endoscopic and non-endoscopic treatment approaches. Thus, the purpose of this review was to present a succinct yet complete review of the literature for non-invasive and invasive treatment approaches for chronic radiation proctitis, and from this data to outline a pragmatic approach to the treatment of radiation proctitis.

LITERATURE SEARCH

A systematic literature search was conducted using the MEDLINE database *via* PubMed for studies of medical,

endoscopic and surgical treatment of radiation proctitis. The search terms were ("Radiation Injuries" [Mesh]) AND ("Proctitis/diet therapy"[Mesh] OR "Proctitis/drug therapy"[Mesh] OR "Proctitis/prevention and control"[Mesh] OR "Proctitis/radiotherapy"[Mesh] OR "Proctitis/surgery"[Mesh] OR "Proctitis/therapy" [Mesh]). The publication range of interest was from January 1st, 1980 until February 29th, 2016 and only citations in written in English and on humans were included. A total of 216 studies were found. Of these 28 were found to be review articles and 65 were clinical trials. Of all of the clinical trials, only 7 were found to be multi-center. An additional 36 case reports and 2 meta-analyses were noted. Twenty-four citations were comments or letters to the editor. In our review, we placed an emphasis on including specific details about randomized controlled trials noted in the literature search.

NON-ENDOSCOPIC MEDICAL THERAPY

Medical therapy should be the initial intervention after conservative management fails. Medical options offer minimal risk when compared to invasive treatment approaches. On current review, randomized controlled data supports butyrate as an effective treatment of acute radiation proctitis, and supports sucralfate, metronidazole and hyperbaric oxygen^[48-51] as effect treatments of chronic radiation proctitis. Considerable prudence should be used with formalin instillation as serious morbidity was noted in one prospective trial^[52]. Table 3 summarizes potential medical therapy for radiation proctitis.

SUCRALFATE

Sucralfate is a highly sulfated polyanionic disaccharide. This medication is thought to affect radiation proctitis *via* two mechanisms. First, sucralfate mechanically protects the gastrointestinal mucosa by forming a protective coating on inner surface of the bowel. Second, it is thought to stimulate healing by increasing angiogenesis^[53].

Numerous studies have been performed using sucralfate in oral and endorectal topical preparation. One of the few randomized controlled double-blind trials in the treatment of radiation proctitis was reported by Kochhar *et al*^[54]. Patients were treated with a 4-wk course of oral sulfasalazine (3.0 g/d) and were randomly assigned to receive prednisolone enemas (20 mg twice daily) or sucralfate enemas (2.0 g twice daily). Patients who were randomized to sucralfate enemas tolerated treatment better and had a superior response compared to prednisolone enemas. The same authors reported this trial with long-term follow up, with a median of 45.5 mo after cessation of bleeding^[55]. This also confirmed the benefit with sucralfate, with a decrease in the number of episodes of bleeding in 77% of patients by week

4 and 92% of patients by week 16. No treatment complications were observed.

However, another randomized, placebo-controlled trial did investigate the delivery of sucralfate *via* an oral route in conjunction with endoscopic argon plasma coagulation, which failed to show a benefit to bleeding control^[56]. Despite these mixed results for the oral preparation, the endorectal topical preparation of sucralfate can be considered an effective medical therapy for radiation proctitis with minimal side effects. Patients should be counseled on twice daily self-administration of sucralfate enema, prepared using two 1 g tablets mixed with 4.5 mL of water to produce a paste-like consistency^[57].

METRONIDAZOLE

Metronidazole is an antibiotic and antiprotozoal medication in the nitroimidazole class, which exerts its effect by inhibiting nucleic acid synthesis of anaerobic and microaerophilic microbial cells. Metronidazole is thought to have an immunomodulator effect as well. Current indications for treatment include pelvic inflammatory disease, giardiasis, amebiasis and *Clostridium difficile* colitis, which are all potential conditions in the differential diagnosis of radiation proctitis.

Two randomized controlled trials have been reported showing benefit to utilizing oral metronidazole in combination with other agents. Cavčić *et al.*^[50], evaluated the efficacy of metronidazole on rectal bleeding and diarrhea. Sixty patients were randomly assigned to treatment with mesalamine plus beta-methasone enemas with or without metronidazole (400 mg orally three times daily). The outcome showed that the incidence of rectal bleeding, mucosal ulcers, diarrhea and edema were significantly reduced in the arm randomized to metronidazole at 4 wk, 3 mo, and 12 mo. A more recent study reported in *Dis Colon Rectum* reported in 2012 randomized 50 patients with chronic radiation proctitis to daily rectal irrigation plus oral metronidazole (3 × 500 mg/d) plus oral ciprofloxacin (2 × 500 mg/d) for a week, or to receive 4% formalin by using proctoscopy^[49]. Compared to formalin, those patients receiving metronidazole plus ciprofloxacin had a significant improvement in rectal bleeding, urgency and diarrhea.

Evidence for the efficacy of metronidazole is some of the strongest we currently have for radiation proctitis. In addition, the medication is widely available, inexpensive, treats common conditions on our differential diagnosis and is relatively safe. Frequent side effects include rash, nausea and vomiting while scattered case reports have described a potentially life-threatening reaction known as Stevens-Johnson syndrome^[58].

medications such as the active agent mesalazine and the prodrug sulfasalazine. They are derivatives of salicylic acid, the active metabolite of aspirin, and act as an antioxidant reducing potentially dangerous metabolic byproducts like free radicals. In addition, they have a well-established anti-inflammatory role, most notably through the reduction of prostaglandin production^[59]. 5-ASA is a bowel specific aminosalicylate with a predominate location of action in the gut, thus reducing systemic side effects. Therefore, they are used to treat inflammatory conditions of the gastrointestinal tract, including ulcerative colitis and Crohn's disease. Acute radiation proctitis is thought to be mediated by eicosanoid pro-inflammatory molecules and thus theoretically 5-ASA may be effective in reducing both inflammation and clinical symptoms of radiation proctitis^[60].

Unfortunately, despite the hypothetical benefit to 5-ASA use, the data has been mixed in support of its efficacy. A small pilot study of four patients with severe and chronic radiation enteritis and/or colitis were treated with 5-ASA derivative (salicylazosulfapyridine) ± oral prednisone^[61]. Treatment was daily for one year and median follow up extended past three years. All patients reported remarkable clinical improvement and 75% showed objective radiographic improvement. Encouraged by these results, the University of Kansas treated four patients with radiation proctitis with a 4 g 5-ASA enema nightly for two to six months^[62]. Surveillance sigmoidoscopy failed to show improvement in mucosal inflammation in any patient. Clinically three patients reported no improvement in bleeding, pain or tenesmus, while one patient had a non-sustained improvement. Because of the small sample size, it is difficult to draw conclusions regarding the efficacy of 5-ASA from these studies.

A more promising recent non-randomized study reported by Seo *et al.*^[63] investigated efficacy of the combination of both oral and endorectal topical mesalazine for radiation proctitis. All patients in the trial were treated with oral mesalazine (3 g daily) plus mesalazine suppository (1 g at bedtime) for 4 wk. Endpoints were patient reported clinical symptoms *via* the SOMA-LENT scale and sigmoidoscopic findings. Compared to pre-treatment scores, a significant improvement was noted in patient reported bleeding, telangiectasia and friable mucosa while pain, tenesmus and stool frequency were not different. The authors conclude this combination treatment may be effective but a randomized controlled trial is needed to confirm this. Given that other medical agents such as sucralfate and metronidazole have shown benefit in randomized trials, 5-ASA derivatives are likely considered second line medical therapy and can be used if first line agents fail.

5-AMINOSALICYLIC ACID DERIVATIVES

5-aminosalicylic acid (5-ASA) derivatives include

PROBIOTICS/ANTIOXIDANTS

Probiotics and antioxidants are some potential

treatment options with the most favorable side effect profile. Probiotics are live bacteria and yeasts that are thought to be beneficial to a person's health when consumed, especially to the digestive system^[64]. Possible proposed mechanisms of action include immune enhancement of phagocytosis, natural killer cell activity and mucosal immunoglobulin A production, as well as antimicrobial activity vs pathogenic intestinal bacteria^[65]. The literature is mixed with respect to the effect of probiotics as prevention of radiation proctitis. A phase II study reported by Scartoni *et al*^[66] included 40 consecutive patients undergoing pelvic radiation who were given a nutritional supplement "Dixentil" (which consisted of zinc, prebiotics, probiotics and B vitamins) as prophylaxis during radiation. Proctitis was noted in 17 patients, and were noted to include only Grade 1 ($n = 14$) and Grade 2 ($n = 3$) toxicity. No control was included in this study. A recent randomized trial from Iran assessed blood counts and serum IgA levels in 67 patients undergoing pelvic radiation^[67]. Patients were randomized to one of three arms to take during radiation: (1) probiotic; (2) probiotic plus honey; or (3) placebo. Samples at the end of radiation therapy were all not significantly different for any of the arms, bringing the systemic impact of probiotics into question.

Antioxidants affect oxidative injury due to free radicals, which is thought to have a role in chronic radiation proctitis. Two small trials (19 and 20 patients, respectively) were performed studying the efficacy of antioxidants. The first trial investigated retinol palmitate, an ester of retinol (Vitamin A), by randomly assigning patients with radiation proctitis to oral retinol palmitate or placebo for 90 d^[68]. Those on retinol palmitate had a significant increase in response compared to placebo, 70% vs 22% percent. The second trial was an uncontrolled trial with patients treated with oral vitamin E (400 IUs three times daily) and oral vitamin C (500 mg three times daily)^[69]. Of the original 20 patients, 10 completed one year of therapy as prescribed, and of these, 100% of these patients reported sustained improvement in their symptoms, though the lack of a control group makes it difficult to draw firm conclusions.

Evidence supporting the use of probiotics and antioxidants is mixed but promising, given the effect noted in small studies and favorable side effect profile. Larger controlled studies are needed to validate these results.

BUTYRATE/SHORT-CHAIN FATTY ACIDS

Butyrate is the name for the conjugate base of butyric acid, a short-chain fatty acid. These compounds are the preferred luminal nutrient for mammalian colonocytes; without butyrates present these cells undergo autophagy^[70]. Probiotic bacterial colonies are the main producer of naturally occurring short-chain fatty acids. The rationale behind the use of butyrate

for the treatment of radiation proctitis is that the acute phase is characterized by superficial epithelial cell depletion. Thus enhancement of short-chain fatty acids may increase epithelial cell resistance and replacement.

Two prospective studies showed that butyrate accelerated healing in the setting of acute radiation proctitis. As reported in *Lancet*, a randomized crossover trial of 20 patients with acute radiation proctitis treated with either 80 mmol/L of sodium butyrate *via* enema or placebo *via* enema showed strong evidence supporting the efficacy of butyrate^[48]. The investigators used clinical, endoscopic and histological findings with a significant difference in nearly every recorded factor. In addition, after the crossover, 8 out of 9 previously treated placebo patients went into remission while 3 of the butyrate patients relapsed. A non-randomized prospective trial examining 31 patients treated with sodium butyrate enemas during acute radiation proctitis showed consistent results^[71]. Toxicity was assessed *via* the Common Toxicity Criteria and 74% experienced a decrease in acute symptoms.

However, butyrate does have apparent limitations to its benefit. A very large ($n = 166$) randomized, placebo-controlled trial examined the role of daily sodium butyrate enemas given for the prevention of acute radiation proctitis^[72]. There was no evidence for this intervention reducing the incidence, severity or duration of acute radiation proctitis. In addition, a randomized, placebo-controlled cross-over trial addressing the efficacy of butyrate in treating chronic radiation proctitis failed to show significant benefit^[73]. Thus, strong randomized evidence exists for the use of short-chain fatty acids *via* topical delivery for the treatment of acute radiation proctitis, as well as against the use for prophylaxis of acute proctitis or treatment of chronic proctitis.

TOPICAL FORMALIN

Formalin is an aldehyde which induces coagulative tissue necrosis on contact. It is commonly used as a tissue preservative due to its ability to cross-link amino groups found in proteins with nitrogen atoms. The rationale for formalin use in radiation proctitis is when applied to tissue with actively growing neovasculature, formalin induces a chemical mediated necrosis, sclerosing these vessels shut^[20]. Endorectal formalin instillation has been used successfully in several studies though a remaining major concern to its widespread adoption is serious treatment-related morbidity^[74].

Complications noted in a four person pilot study by Pikarsky *et al*^[75] included one patient with severe anococcygeal pain and fecal incontinence and another patient with post-procedural formalin-induced colitis needing admission and intravenous antibiotics. A larger, prospective single-armed study of 33 patients with chronic refractory radiation proctitis found after

Table 4 Endoscopic therapy for radiation proctitis

	Proposed mechanism	Indications
Dilatation	Mechanical	Single institution studies support treatment of stricture, no RCT to date
Bipolar cautery and heater probe	Thermoelectric cauterization	RTC supports treatment of chronic proctitis
Nd:YAG, KTP laser	Coherent wavelength of electromagnetic radiation	Single institution studies support treatment of chronic proctitis, no RCT to date
Radiofrequency ablation	Rapidly alternating radiofrequency waves	Single institution studies support treatment of chronic proctitis, no RCT to date
Argon plasma coagulation	Noncontact electrocoagulation	RTC supports treatment of chronic proctitis, largest amount of data

Nd:YAG: Neodymium/yttrium aluminum garnet argon; KTP: Potassium titanyl phosphate; RCT: Randomized controlled trial.

one or two instillations of formalin almost 40% of patients had complete resolution of bleeding and another 30% had near complete control^[76]. Despite these promising results, the authors conclude that local morbidity is a real concern, as 18% of the patients underwent stricture formation and 21% had increasing fecal incontinence.

Additional toxicity was reported in the *Journal of Surgical Oncology* in a cohort of 20 patients with radiation proctitis all treated with 4% formalin instillation^[52]. The overall success of bleeding control was 90% with the vast majority of patients only needing one instillation. Despite this 5 patients had moderate post-procedural pain and another patient developed rectosigmoidal necrosis requiring resection with Hartmann procedure. Additionally, 2 more patients developed a rectovaginal fistula requiring colostomy, with eventual abdominoperineal resection due to pelvis sepsis in one of the two. Thus effective, the rate of Grade 4 toxicity approached 20% in this group which is certainly cause for hesitation in endorsing formalin as treatment of radiation proctitis. Therefore, formalin may be best suited for patients with proctitis refractory to less toxic endoscopic therapy, like argon plasma coagulation, rather than as an upfront approach.

HYPERBARIC OXYGEN

Hyperbaric oxygen (HBO) is a medical treatment which enhances the innate healing abilities of a person through the inhalation of 100% oxygen, delivered in daily fractions over a period of weeks *via* a full body chamber with increased atmospheric pressure. HBO induces the regrowth of damaged vascular endothelial cells and improves the activity of antioxidant enzymes thereby reducing free-radical damage^[51,77]. Chronic radiation proctitis is thought to be mediated by small vessel vasculopathy leading to secondary changes such as submucosal fibrosis. Thus, HBO is an attractive treatment modality given its reparative effects on

damaged blood vessels.

The strongest evidence supporting HBO comes from a single randomized controlled trial^[78] and a systematic review^[79]. Clarke *et al*^[78] reported in *International Journal Radiation Oncology Biology Physics* a randomized trial with 120 evaluable patients who either underwent HBO at 2.0 atmospheres or sham treatment with subsequent crossover of the sham arm to the treatment arm. The outcomes analyzed were the SOMA-LENT score and quality of life. At initial analysis the patients treated with HBO had a significant improvement in SOMA-LENT and quality of life scores, as well as a greater portion of responders (88.9% vs 62.5%). After crossover, these differences were no longer significant. The systematic review of 74 publications, as reported by Feldmeier *et al*^[79], found that 67 of the articles reported a positive result for the treatment of chronic radiation proctitis, while the remaining 7 found no benefit. In addition, the authors argue that HBO possibly delays or precludes more invasive intervention. However, a recent trial conducted by Glover *et al*^[80] reported results contradicting these previous studies. This trial randomized 88 patients with chronic bowel dysfunction following pelvic radiotherapy to either HBO or sham control. HBO failed to significantly improve patient-reported bowel quality of life or rectal bleeding compared to sham control. Given the mild and transitory common side effects of HBO such as, anxiety, otic barotrauma and temporary myopia, as well as its questionable efficacy it can be considered an alternative to more invasive treatments in a patient failing medical management.

ENDOSCOPIC THERAPY

The goal of endoscopic therapy is to provide cessation of rectal bleeding, decrease the need for transfusion or hospitalization, and thus improve the patient's quality of life. These techniques should be considered after medical management has failed, and the patient experiences persistent symptoms. Endoscopic therapy is not without risk, both in the application of sedating agents and through the procedure itself. A discussion regarding the potential risks and benefits prior to any procedure will help management expectations. On current review, randomized controlled data supports argon plasma coagulation and bipolar cautery/heater probe as an effective treatment of chronic radiation proctitis, while single institution studies also support laser and radiofrequency ablation. Details are summarized on Table 4.

DILATION

Though a less common presentation, patients with radiation proctitis can develop a lower gastrointestinal stricture with resultant obstructive symptoms. Mechanical dilation *via* an endoscopically passed balloon

is a simple but effective treatment for patients with radiation-induced rectal strictures^[81]. Complications for treatment are minimal and patient benefit from an immediate correction of their underlying obstructive symptoms. The risk of perforation is increased in patients with long or angulated strictures. Although, it is important to note that dilation plays no role in the treatment of rectal bleeding. The treatment of lower gastrointestinal strictures is less well reported in the literature, as the vast majority of data on the dilation of radiation-induced strictures is for esophageal^[82] and urethral^[83] sites.

BIPOLAR CAUTERY AND HEATER PROBE

Bipolar cautery probes achieve hemostasis *via* passing electricity through the alternating arrays of the positive and negative electrodes at the tip of the probe. This causes heating, which in turn causes tissue coagulation once the temperature reaches above 60 °C. Direct contact is necessary for successful cauterization. The heater probe is a separate cautery device, which has a thermocouple located at the ceramic tip of a probe which rapidly heats. The depth of penetration of the heater probe is not limited, and deep coagulation is possible. This makes the heater probe more susceptible to serious complications like perforation. Despite this, a benefit of these two devices is their wide availability and relative inexpensiveness.

One of the first reported investigations on bipolar cautery was a small, retrospective study in *Gastrointestinal Endoscopy* by Maunoury *et al*^[84]. Four patients with chronic radiation proctitis were treated with between 3 to 5 sessions of bipolar electrocoagulation at a power setting of 50 W. Symptoms completely resolved in all of the patients with a maximum follow up of 45 mo. Jensen *et al*^[85] reported on a randomized prospective trial with 21 patients, who were all first treated with 12 mo of medical management, followed by up to four sessions of either endoscopic bipolar electrocoagulation or heater probe treatment. Severe bleeding significantly decreased in both the bipolar cautery arm and the heater probe arm when compared to the results of medical management over the prior 12 mo for each group (75% vs 33%, and 67% vs 11%, respectively). In addition, the mean hematocrit rose significantly for both arms. During long-term follow-up, new telangiectasias or rectal bleeding were easily controlled and no major complications resulted.

A randomized controlled trial comparing bipolar cautery and argon plasma coagulation for patients with chronic radiation proctitis was reported by Lenz *et al*^[86]. Thirty patients, all with active bleeding, were randomly selected for one treatment modality and success was defined as eradication of all *via* ble telangiectasias. Both treatments were found to be equally effective with only one failure per group, and

no differences were observed in number of sessions or relapses. Bipolar cautery was associated with a significantly higher rate of complications than the argon plasma coagulation group. Thus, bipolar cautery has been shown in small studies to be safe and effective for chronic radiation proctitis.

Nd:YAG AND KTP LASER

Medical lasers are devices that emit a coherent wavelength of electromagnetic radiation with the purpose of coagulating or ablating tissue. The Nd:YAG laser and KTP laser have been used to coagulate bleeding vessels in the gastrointestinal tract. Nevertheless, laser treatment has disadvantages compared to other endoscopic interventions due to its high cost and inability to control the depth of penetration, which may increase risk of perforation. Thus, at the current time these devices are not commonly available. Given these factors, a limited number of trials have been reported on laser therapy for radiation proctitis.

Barbatzas *et al*^[87] reported a single institution study on 9 patients with chronic radiation proctitis who were treated with an average of 3 sessions of Nd:YAG laser. Bleeding was reduced to only occasional spotting in 66% of the patients and the need for transfusion was also decreased. No significant complications were reported. A larger single institution experience was reported by Viggiano *et al*^[88]. The authors reviewed 47 patients with radiation proctitis, of which nearly 100% had failed medical therapy. Within 6 mo of Nd:YAG laser treatment, the number of patients with daily rectal bleeding fell from 85% to 11%, which was highly statistically significant. In addition, the median hemoglobin level increased from 9.7 gm/dL to 11.7 gm/dL, also significant. Complications were reported in 3 patients and none were fatal.

More recently, there has been additional interest in the KTP laser for radiation proctitis due to its favorable treatment parameters over the Nd:YAG laser. The KTP laser beam is created by passing the Nd:YAG laser through a crystal which reduces the wavelength of the emitted light to 532 nm. This wavelength is preferentially absorbed by hemoglobin and has a more shallow depth of penetration (max 2 mm) compared to the unmodified Nd:YAG laser. In theory, this reduces the risk of transmucosal injury and subsequent necrosis or perforation. Taylor *et al*^[89] reported on 23 patients with radiation proctitis treated with a median of 2 sessions of KTP laser. After treatment there was a statistically significant improvement in frequency of rectal bleeding, hematocrit levels, activities of daily life and utilization of health care resources. Complications were mild with two patients developing rectal ulcers. Thus both laser units appear effective and relatively safe for the treatment of radiation proctitis, but no randomized controlled trials exist to confirm this.

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) utilizes a needle electrode to transmit an alternating radiofrequency current into the tissue adjacent to the electrode's tip. The ions in the adjacent tissue attempt to change direction following the alternating current, which produces movement with resultant frictional heating. As the tissue temperatures rise above 60 °C, the cells in the region of the electrode necrose^[90].

RFA only recently has been utilized to treat chronic radiation proctitis, having been mostly relegated to treatment of liver malignancy^[92] or Barrett's esophagus^[92]. One of the first examples of RFA to treat radiation proctitis was reported by Zhou *et al.*^[93]. The authors report on a pilot trial with 3 patients whom had hemostasis achieved after 1 or 2 RFA sessions. Endoscopic surveillance confirmed re-epithelization of squamous mucosa over the areas of prior hemorrhage and no stricture or ulceration formation 19 mo after treatment. Since this study, a handful of similar studies with equally small patient numbers have reported similar results^[94]. But the largest study to date on RFA was reported by Rustagi *et al.*^[95] and included 39 patients. All patients experienced complete resolution of rectal bleeding after a mean follow up of 28 mo. The most frequently reported side effects were mild-to-moderate anorectal pain, temporary fecal incontinence and perianal ulceration. Though promising, no randomized controlled trials have been conducted on RFA to date, limiting generalizations about its future adoption.

ARGON PLASMA COAGULATION

Argon plasma coagulation (APC) is a non-contact thermal method of coagulation and hemostasis. It was designed to be an alternative to direct contact coagulation, with the advantage of increased safety due to a controllable depth of treatment penetration (maximum 2-3 mm). This modality utilizes a jet of sprayed argon gas, which is ionized by a high voltage spark into plasma. Once ionized, the plasma seeks a ground in the nearest tissue, and in doing so deposits thermal energy. Care must be exercised to not discharge the argon plasma probe too close to the mucosal target, as any inadvertent contact causes a deeper injury similar to direct-contact coagulation (like bipolar cautery).

APC remains one of the techniques most commonly reported on for the treatment of radiation proctitis, with a recent review showing around 80% of all current endoscopic-specific literature conducted on APC^[96]. Few head-to-head comparative trials have been performed on any treatments for radiation proctitis, though two have been reported in the literature between APC and formalin. First, a study by Alfadhli *et al.*^[97] retrospectively compared outcomes for 22 patients who were treated with APC alone (n

= 11), formalin instillation alone ($n = 8$) or both ($n = 3$). Patients treated with APC had a significantly improved chance for control of rectal bleeding while those treated with formalin had an increased likelihood of adverse events including nausea, vomiting, cramps and rectal pain. The second study, by Yeoh *et al.*^[98], reported on 30 men with intractable chronic proctitis after receiving radiation for prostate cancer. All men were randomized to APC or topical formalin. The treatment endpoint, reduction in rectal bleeding to at most once monthly, was achieved in 94% of the APC group and 100% of the formalin group after a median of 2 sessions in either arm. There were no differences between side effects of the two treatments, including anorectal symptoms or function.

Besides these comparative studies, the overwhelming majority of other trials include single institutional experiences. Swan *et al.*^[99] reported on a large ($n = 50$), prospectively gathered non-randomized study evaluating the efficacy of APC for patients with chronic radiation proctitis. One third of the patients had failed prior therapy before APC administration. Minor or no rectal bleeding was noted in 68% of patients after 1 session and 96% after 2 sessions. Only one patient experienced a long-term complication from treatment. Silva *et al.*^[100] reported parallel results on 28 patients in a prospectively collected non-randomized trial. Again, around one third of patients had failed prior treatment before APC. The authors report that the severity of bleeding decreased while the average hemoglobin level increased 1.9 gm/dL in anemic patients. Serious complications were not observed.

A novel animal-based exploratory trial from Japan by Sato *et al.*^[101], sought to determine the optimal APC settings for the ideal depth of penetration. They investigated various power settings (20, 40, 60 and 80 W) and variable application times (1, 2, 3 and 4 s) with a fixed argon gas flow rate of 1.2 L/min. Results showed that a power of 40 W, with single pulses up to 2 s allowed for the desired combination of sufficiently treated submucosal telangiectasia without affecting the deeper underlying muscle layer. Using this information, the authors then conducted a prospective non-randomized trial on 65 patients with chronic radiation proctitis. APC was successful in 98.5% of the patients after a median of 2 sessions, and the post-APC hemoglobin level significantly increased as well.

APC is a fairly safe interventional treatment, with post-procedural complications usually minor and self-limited, with the exception of the formation of strictures, rectal ulcers or perforation. Most reports suggest that any complication occurs in 5% to 20% of APC cases^[102], though isolated reports suggest higher rates. An uncontrolled prospective study of 27 patients treated in Milan, Italy specifically reviewed complications of APC and reported fever and pain in 7% of the patients, but rectal ulcer formation in 52% of the patients^[103]. Patients were completely asymptomatic with respect to the rectal ulcers and half of the noted

Table 5 Surgical therapy for radiation proctitis

	Proposed mechanism	Indications
Diverting ostomy	Diversion of fecal stream allows for healing	Single institution studies support treatment of chronic radiation proctitis if refractory to medical and endoscopic measures, moderate morbidity and mortality associated
Local excision/flap reconstruction	Removal of poorly vascularized tissue and replacement with well perfused tissue	Little data exists to support the routine use of excision and reconstruction for patients with radiation proctitis
Proctectomy/exenteration	Removal of damaged tissue	Single institution studies support treatment of chronic radiation proctitis if refractory to medical and endoscopic measures, significant morbidity and mortality associated

ulcers endoscopically resolved without intervention after a mean of 141 d post-procedure. Other causes have been indicated in the increased possibility for post-APC ulcer formation, such as excessive use of NSAIDs or malposition of brachytherapy seeds^[104].

Thus APC has a strong track record with a large body of evidence supporting its efficacy in the cessation of bleeding due to chronic radiation proctitis, and is generally tolerated very well with the exception of rare, but serious complications. If available, this makes APC the preferred initial choice of endoscopic intervention.

SURGICAL THERAPY

Surgical approaches represent the most invasive treatment for radiation proctitis (Table 5). Thus, these interventions should be reserved for those patients with either symptoms refractory to medical and endoscopic therapy or for patients with symptoms such as brisk hemorrhage, perforation, fistula or obstructing stricture. The need for such intervention is quite rare, and utilization is estimated to be less than 10% of all patients with radiation proctitis^[105].

DIVERTING OSTOMY

For some patients with radiation proctitis, continued passage of the fecal stream can aggravate symptoms such as pain, tenesmus, drainage and infection. The creation of a temporary diversion has been shown to help reduce these symptoms by decreasing bowel irritation. Quality of life before and after diversion was studied in several reports. Pricolo *et al.*^[106] reported a 30-year review of the experience at a single institution including 60 patients treated with diverting ostomy in addition to other surgical approaches. Quality of life was examined and for some patients a diversion was so effective additional intervention was no longer needed.

Somewhat surprisingly, though not addressing the underlying cause of rectal bleeding, diverting ostomy has been shown to also decrease bleeding. A small study on nine patients by Ayerdi *et al.*^[107] showed no operative complications and 88.9% of the patients had cessation of bleeding as well.

This procedure is commonly performed in the United States, with approximately 100000 patients per year undergoing an operation for colostomy or ileostomy, though the vast majority of these patients do not have radiation proctitis^[108]. Despite being commonly performed, reports of postoperative complications run as high as 70%^[109], with 30-mortality for non-emergent cases estimated to be 5.9%^[110]. Thus, before considering diverting ostomy for the treatment of radiation proctitis, the potential risks and alternatives should be considered.

LOCAL EXCISION/FLAP RECONSTRUCTION

It has been well established that chronic radiation proctitis is due to small vessel vasculopathy, and that post-irradiated tissues suffer from abnormal and damaged vasculature which can compromise future healing^[28]. Thus, a local excision with reconstruction *via* mobilization of an advanced flap is theoretically very appealing as it simultaneously both removes poorly vascularized tissue and replaces it with well-perfused healthy tissue. Although this procedure is possible, outcomes reported in the literature have been marred by unacceptable long-term morbidity and flap failure^[111]. Attempts to overcome some of these complications have been noted through the use of sphincter reconstruction with a gracilis myocutaneous flap, but incontinence and stricture formation have nevertheless been noted^[112]. Little data exists on excision with reconstruction and the decision to attempt such a procedure should be made on a case-to-case basis, with active involvement from the patient.

PROCTECTOMY/PELVIC EXENTERATION

In patients with persistently refractory radiation proctitis, the most extreme intervention is complete rectal excision with possible removal of adjacent pelvic organs. This intervention should only be offered to patients who have either exhausted all other medical, endoscopic and surgical approaches or who present with an acute life-threatening situation. Patients who are considered a candidate for this procedure commonly have a greatly reduced quality of life due to intractable pain, fecal incontinence or serious bleeding. This treatment can be considered the most definitive treatment for radiation proctitis, in that it removes the offending tissue and gives fecal diversion though a permanent ostomy. Correspondingly, the

literature reports a significant risk of morbidity, 15%-80% and mortality, 3%-9% associated with this procedure^[105,113-115]. High rates of anastomotic leaks and perineal wound complications have also been noted^[116].

CONCLUSION

Radiation-induced proctitis is a relatively common yet challenging adverse event for patients with pelvic malignancy. As treatment strategies advance and survival rates increase, practitioners will likely see a corresponding growth in patients presenting with the common constellation associated with radiation proctitis: diarrhea, urgency, rectal bleeding and/or fecal incontinence. In some patients, the symptoms are mild and self-limited though for others the symptoms can be brisk and life threatening. Treatment options include observation, medical management, endoscopic intervention and even surgical approaches. As for any condition, management decision making is ideally guided by randomized controlled data, with head-to-head comparisons of the various treatment options. Unfortunately, there is a lack of such data for radiation proctitis and thus management is guided mainly by small randomized trials and single institutional studies.

After reviewing the existing data, we believe that treatment should be escalated corresponding to the patient's clinical status, keeping in mind the known toxicity of each potential treatment. Most mildly symptomatic patients can attempt medical management for either acute (*i.e.*, butyrate enema) or chronic radiation proctitis (*i.e.*, sucralfate enema, metronidazole or HBO). Once a patient has failed this approach and remains symptomatic, endoscopic treatment (*i.e.*, APC) should be considered. Patients who fail endoscopic intervention or who become clinically unstable due to profound hemorrhage should be considered for surgical approaches.

The treatment of radiation proctitis is an evolving field, and we welcome new high quality comparative studies among medical, endoscopic and surgical approaches to define the future standard of care for our patients.

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ISSN 1007-9327

