Management and Course

- Most patients with IC improve with conservative measures that optimize cardiovascular function.
- Unlike for nonocclusive mesenteric ischemia, vasodilation agents have not proved useful in treating IC.
- Vasoconstricting agents and volume depletion should be avoided.
- If patients deteriorate clinically or demonstrate frank peritonitis, emergency surgical exploration is required and all necrotic segments should be resected.
- Similarly, patients with symptomatic colonic strictures should undergo elective resection.
- Revascularization is not indicated for IC.
- Although a small percentage of pts. succumb to complications of IC, survival is most often limited by the acute illness precipitating the compromised colonic perfusion.

Medications That Produce Colonic Ischemia

- Oral contraceptive use (10 days to 11y) is associated with mesenteric arterial and venous thrombosis, typically presenting as IC.
- Estrogen produces hypercoagulability, mesenteric vasospasm, and endothelial proliferation with subendothelial fibrosis.
- Vasopressin causes colonic ischemia by reducing blood flow whereas
- Cocaine and dextroamphetamine evoke intense mesenteric vasospasm.
- Ergot preparations produce colonic vasospasm, whereas Ergotamine suppositories can cause rectal ulcers with obliteration of small blood vessels, endothelial proliferation, and thickening of the vascular wall.
- IC has been reported after the use of neuroleptic and tricyclic antidepressants.
- Digitalis Preparations are associated with colonic ischemia, in part because of the underlying low-flow states (e.g. CHF) that produce **colonic hypoperfusion.**
- These agents produce mesenteric vasoconstriction in animal models however, and may directly contribute to consequent ischemia.

iii) Escherichia coli 015:H7-Associated Colitis[37]

- This syndrome was recognized in the early 70s before an etiology was found and reported under names such as evanescent colitis, transient ischemic colitis or transient hemorrhagic colitis. Since its description as a cause of hemorrhagic colitis (HC) in 1983, Escherichia coli (E. coli) 0157:H7 has been increasingly recognized as an important pathogen.

- E. coli serotype 0157:H7 was first isolated in 1982, when 47 persons in Michigan and Oregon developed bloody diarrhea after eating hamburgers contaminated with the organism. Retrospective contamination of more than 3000 E. coli cultures obtained between 1973 and 1982 has found only one isolation with serotype 0157:H7; it was from a 50-y-old woman who had had an episode of acute, self-limited, grossly bloody diarrhea in 1975. Since the initial reports, sporadic cases and outbreaks of E. coli 0157:H7 infection have increasingly been reported, and surveillance and prospective studies to identify and characterize disease associated with E. coli 0157:H7 have been started in the U.S. and abroad.

- Infection with E. coli 0157:H7 presents with a wide spectrum of clinical manifestations. These include asymptomatic carriage, only nonbloody diarrhea, severe abdominal cramps with little or no fever and watery diarrhea that often progresses to grossly bloody diarrhea. Extraintestinal involvement, including cardiac and neurologic manifestations, has been reported and infection can be associated with serious conditions such as the hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura. The disease can be fatal.

- Not only is E. coli 0157:H7 an important agent for hemorrhagic colitis, it is also one of the leading causes of bacterial diarrhea.

- Patients at extremes of age have an increased risk for infection and associated complications.

- Transmission of E. coli 0157:H7 is primarily food-borne. Undercooked meat is the most common culprit, and secondary person-to-person spread is also important.

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[37] [P.M. Griffin et al., Escherichia coli 0157:H7-Associated Colitis. A clinical and Histological Study of 11 cases. Gastroenterology 99:142-149 (1990)]
[K.J. Morris, G.G. Rao Conventional screening for enteropathologic Escherichia coli in the UK. Is it appropriate or necessary?, J. Hosp. Infect. 21:163-167 (1992)]
[C. Su and L.J. Brandt. Escherichia coli 0157:H7 Infection in Humans Ann. Intern. Med. 123:698-714 (1995)]
[R. Gonzalez et al. Age-specific prevalence of Escherichia coli with localized and aggregative adherence in Venezuelan infants with acute diarrhea. J. Clin. Microbiol. 35:1103-1107 (1997)]
[T.I. Baldwin The 18th C.L. Oakley Lecture. Pathogenicity of enteropathogenic Escherichia coli. J. Med. Microbiol. 47:283-293 (1998)]
[N. Porat et al. Prevalence of intestinal infections caused by diarrheagenic Escherichia coli in Bedouin infants and young children in Southern Israel. Pediatr. Infect. Dis. J. 17:482-488 (1998)]
N.T. Perna et al. Molecular evolution of a pathogenicity island from enterohemorrhagic Escherichia coli 0157:H7. Infect. Immun. 66:3810-3817 (1998)]
[C Su et al. The immunological diagnosis of E. Coli 0157:H7 Colitis: Possible Association with Colonic Ischemia. Amer. J. Gastroenterol. 93:1055-1059 (1998)]

- The organism produces at least two shiga-like toxins that differ antigenically, physicochemically, immunologically, and in their biological effects. These toxins are thought to have direct pathogenic significance in E. coli 0157:H7 infection.

- Direct stool detection or culture of E. coli 0157:H7 remains the preferred approach to its diagnosis. Thus, this infection is usually **diagnosed from a POSITIVE STOOL CULTURE, from the presence of Shiga-like toxins or both.** [Timely collection (within 7 days of illness onset) of a stool sample for culture is imperative for a high recovery rate]. **If infection is confirmed, it should be reported to public health officials.**

- Radiological and colonoscopic changes range from a normal appearance to mucosal and submucosal hyperemia, edema, erosions, ulceration, and hemorrhage; bowel wall thickening mainly affects the ascending and transverse colon.

- Microscopically, E. coli 0157:H7-associated colitis can resemble a combination of **colonic ischemia** and of infections and toxic injury similar to that seen in colostridium difficle-associated pseudomembranous colitis. Submucosal hemorrhage, edema, and fibrin exudation are the most prominent features; other less common lesions include ulceration, hemorrhage, capillary thrombi, and mild neutrophil infiltration of the mucosa.

- Currently, the diagnosis of infection with E. coli 0157:H7 is established by finding sorbitol nonfermenting colonies on MacConkey-sorbitol agar that react with 0157 and H7 antisera.

- Because the hemorrhagic colitis of E. coli 0157:H7 infection in older adults is frequently indistinguishable from COLONIC ISCHEMIA in its presentation, colonic ischemia is often the initial diagnosis until **the organism is detected by stool culture.**

- Because of the similarities between ischemic and hemorrhagic colitis (of E. coli infection), Su et al. [Amer. J. Gastroenterol. 93:1055-1059 (1998)], have proposed that, in a subset of elderly patients, colonic ischemia is associated with, and possibly precipitated by, the infection. Demonstration of such an association, however, is problematic, as a retrospective diagnosis using stool culture is not possible and identification of the organism is not routinely performed in most clinical microbiological laboratories.

- In an attempt to assess retrospectively the presence of the bacteria in patients with colitis, Su et al. [Locus cited] (1998)], developed an immunohistochemical approach to its diagnosis using histological sections from archival formalin-fixed, paraffin-embedded tissue and immunospecific antisera that readily detected the bacteria in known, culture-proven cases of colitis. To determine whether a relationship exists between infection with the bacteria and colonic ischemia, sections from cases of colonic ischemia as well as other forms of colitis (idiopathic IBD and antibiotic-associated pseudomembranous colitis) were then evaluated for the presence of the bacteria.

- Both cases (100%) of E. coli 0157:H7 colitis and 3 of 11 (27.3%) cases of IC stained positive by light microscopy. In one culture-proved case, electron microscopy demonstrated staining of bacillary structures; in 2 cases of colonic ischemia, extensive

deposits of chromagen material were present that were associated neither with inflammatory cells nor with bacterial forms.

- Su et al. concluded that immunoperoxidase staining of archival sections may be used to diagnose E. coli 0157:H7 infection: an etiological role for this organism is possible in some cases of colonic ischemia. In this study, with this staining procedure, the finding of the bacteria in several cases diagnosed clinically as colonic ischemia, is meaningful. In conclusion, in a subset of patients, **colonic ischemia may have an infectious etiology**.

iv) Ischemic Colitis in the Alosetron Safety Database

In his safety review, Dr. Senior called attention to a "syndrome of constipation, abdominal pain, and rectal bleeding not accounted for by known causes of rectal bleeding (hemorrhoids, menstrual bleeding)". He attributed the syndrome to **ischemic colitis**, which was diagnosed by colonoscopy, in all three patients, one in each of three controlled trials. To these, a fourth case was reported by the sponsor on November 12, just prior to November 16 meeting of the GI Advisory Committee.

GlaxoWellcome called our attention to the fact that Dr. Kay Washington (Vanderbilt University) had carried out histopathological evaluation of all four cases so far reported as ischemic colitis. In this section of my review I first reproduce the clinical summaries for the 3 cases described by Dr. Senior and the additional cases presented at the Advisory Committee meeting. I then highlight the similarities and dissimilarities between the cases from the clinical, colonoscopic and histopathological viewpoints, incorporating Dr. Washington's information where applicable. The aim of this approach is to further characterize these four colitis cases.

a. Clinical Summaries (Table 14)

NOTE: To facilitate comparisons, inclusion of Dr. Wshington's information and possible conclusions, the cases are identified as:

Pt. No.	Study No.	Case I.D.
2829	S3BA2001[a]	The 1996 case
7195	S#BA3002[b]	The 1998a case
15687	S3BA3001[c]	The 1998b case
34069	S3B30011[d]	The 1999 case

a) One of the two Phase II dose-ranging studies (PL vs 1, 2, 4 or 8 mg case ALOS b.i.d.)
b) and c) The two principal Phase III trials.
d) New trial

TABLE 14
NDA 21-107

Concise Clinical Summaries of the 4 Cases of Colitis in the Alosetron Safety Database

Patient #2829, Study S3BA2001
The 1996 Case

- 33 year-old Caucasian woman
- 2 mg bid alosetron for 2 days, starting 17 Jul 96
- severe abdominal pain, 30 watery stools that day
- nothing found on exam in E.R., Levsin given
- pain worse, peritoneal signs, admitted
- colonic mucosal erosions at 40-80 cm
- ischemic colitis diagnosed, withdrawn from study
- gradually recovered over the next 11 weeks

Patient #15687, Study S3BA3001
The 1998b Case

- 41-year-old Caucasian woman
- 1 mg bid alosetron for 54 days, starting 15 Jul 98
- abdominal pain, rectal bleeding; seen in E.R.
- did not respond to hyoscyamine; admitted
- severe segmental colitis[a]
- biopsy indicated ischemic colitis; withdrawn
- gradually recovered over subsequent weeks

Patient #7195, Study S3BA3002
The 1998a Case

- 48-year-old Caucasian woman
- 1 mg bid alosetron, for 39 days, starting 21 Jan 98
- rectal bleeding and crampy abdominal pain
- local doctor prescribed fluid and fiber
- did not respond, pain worse, admitted at 3 a.m.
- colonoscopy showed mucosal sloughing
- ischemic colitis not attributed to study drug
- withdrawn, no more episodes of rectal bleeding

Patient #34069, Study S3BA30011
The 1999 Case

- 61-year-old Caucasian woman
- 7 days of treatment with 1 mg bid alosetron
  - severe abdominal pain (10/28/99)
  - bloody diarrhea
  - WBC 19,700
- CT Scan (10/29/99)
- Mural thickening entire tranisverse colon, descending colon, hepatic flexure
- Changes were consistent with colitis but ischemic colitis was considered unlikely (IMAEt SMA)
- Colonoscopy (11/2/99)
  - Distal transverse to descending colon: patchy areas of edematous hyperemia adjacent to pale areas
  - Bx
  - D/C (11/03/99)

a) Reviewer's correction. Upon colonoscopy this patient (see Table 15) had segmental colitis involving the distal transverse, the descending colon, starting at 50 cm in the proximal sigmoid colon, not the right (ascending) or proximal transverse colon, as erroneously stated in the Safety Review.

b. Clinical Presentations: Similarities and Dissimilarities (Table 15)

The main reason for this comparison is an attempt to identifying a syndrome, common to all four cases regarding clinical presentation of these colitis cases [CONCLUSION: No syndrome was identified]. This conclusion is based on all pertinent information made available by the sponsor, including histopathological assessments carried out by Dr. Kay Washington (Vanderbilt University). The detailed discussion will consider at least three categories of diagnosis: a) clinical, which, of course includes results of x-ray and laboratory tests, b) endoscopic which included either a sigmoidoscopy and/or a total colonoscopy and finally c) a confirmation of the clinical-endoscopic diagnosis by evaluating histopathologic results of biopsy samples taken during the endoscopic procedure. Note that not all patients underwent subsequent colonoscopies/colonic biopsies. This reviewer is concerned, primarily, with information obtained at a time as close as possible to the initiation of the clinical adverse event (refer to Table 15).

- Clinically, the AE(s) occurred in relatively young female patients, as young as 33 years and early elderly (61y of age).

- It occurred in apparent temporal association with alosetron (but no association with placebo was reported) and began anywhere from 2 (the 1996 patient) to 54 days (the 1988b patient) after the starting of test medication.

- The AE was primarily characterized by **rectal bleeding** accompanied by abdominal pain of varying severity, at times (the 1996 patient) with concurrent peritoneal signs and sometimes (2 of the 4 patients) with leukocytosis, most (if by not all) times with diarrhea (NOT CONSTIPATION), and sometimes with fever.

- Information from radiological examinations is not very helpful in that these were not done in two of the four patients. In the 1996 patient, a flat plate of the abdomen revealed no evidence of free perforation. In the CT scan done in the 1999 patient, lots of information is reported, including mural thickening of the entire transverse colon, descending colon, hepatic flexure and all of this is compatible with colitis.

Up to now, all of this clinical information is compatible with the diagnosis made by each of the individual investigators: ISCHEMIC COLITIS. It cannot be concluded however, that they were induced by alosetron.

TABLE 15
NDA 21-107

Comparison of the Clinical, Key Laboratory, Endoscopic and Histopathologic Findings in Alosetron-treated Patients Developing Colitis in Randomized Clinical Trials

Case Age of Patient (years)	1996 (2 mg b.i.d.) 33	1998a (1 mg b.i.d.) 48	1998b (1 mg b.i.d.) 41	1999 (1 mg b.i.d.) 61
Time to AE (days)	2 (07/17/96)	9 (01/21/98)	54 (09/06/98)	7 (10/28/99)
Occurred during outbreak of E. coli infection	NO	NO	NO	NO
Abdominal pain	YES (severe)	YES (Crampy)	YES	YES (severe)
Peritoneal signs	YES	NO	NO	Not Reported
Fever	NO	YES	NO	NO
Rectal bleeding	YES (also Hemoccult +)	YES (Also hematochezia)	YES	YES
Diarrhea	YES	NO	YES	YES
Leukocytosis	NO (WBC 9,900)	YES (17,500)	NO(10,300)	YES (19,700)
Constipation	NO	YES	NO	NO
Stool Culture	96/24/96 • No enteric pathogens. identified, including salmonella, shigella, E. coli 0157:H7, yersinia or campylobacter • No C. difficile toxin detected	02/13/98 • No salmonella, shigella, yersinia, campylobacter or E. coli 0157 isolated. •Negative for C. difficile toxin	Not Reported	Not Reported • Negative for Ova and Parasites • Negative for Clostridium Difficile Toxin A
Hospitalization	YES	YES	YES	YES (?)
X-ray, CT scan	Flat plate of the abdomen revealed no evidence of free perforation	NOT DONE	NOT DONE	10/28/99 (Flat plate abdomen-upright) • Non-specific, non-obstructive bowel gas pattern • 10/29/99 (CT scan) mural thickening entire transverpe colon, descending colon, hepatic flexure, compatible with colitis
Immunohistochemistry for E. Coli 0157:H7				
(a) H&E	YES	YES	YES	YES
(b) Paraffin Embedded	YES	YES	NOT DONE	YES
Classification	-	Infectious	Infectious	+
(a) H&E	-	+	Not Done	-
(b) E. coli				

Withdrawn from trial Investigator's diagnosis Considered differential diagnosis	YES ISCHEMIC COLITIS Less likely, infectious vs IBD	YES ISCHEMIC COLITIS "Secondary causes for ischemic colitis will likely need to be evaluated"	YES ISCHEMIC COLITIS Crohn's diseae or "self-limiting colitis.	YES (11/03/99) ISCHEMIC COLITIS CT scan: Infectious or Inflam. colitis is considered the most likely.
Diagnosis on discharge	Probable Ischemic colitis	Abdominal pain and hematochezia secondary to Ischemic colitis	LLQ pain and rectal bleeding secondary to apparent Ischemic Colitis	IC is felt to be unlikely given the involvement of multiple vascular territories (IMA and SMA) but cannot be completely excluded on the basis of this examination
Evolution Resolved without sequelae	Improved YES	Improved YES	Improved YES	Improved YES
MAIN SIGMOIDOSCOPIC/COLONOSCOPIC FINDINGS				
	07/22/96 • Normal mucosa from the rectum to ca. 40 cm • At 40 to 80 cm was edematous mucosa with scattered erosions and edema; the erosions had some friability with a small amount of white exudate ➞ consistent with ISCHEMIC MUCOSAL TYPE INJURY	02/14/98 • Normal transverse and part of the proximal descending • At about 60 cm insertion, there were changes in the mucosa surface consistent with ISCHEMIC COLITIS • The mucosa was sloughing in some areas and ulcerating and was quite inflammed. • Involvement was down to 30 cm insertion in the mid-sigmoid colon. This area was quite painful to pass the scope through for the patient. • The distal sigmoid and rectum was not involved. • There was no active bleeding seen going on, except at the biopsy sites.	09/08/98 • Beginning at 50 cm in the proximal sigmoid colon there were streaks of erythema and erosions and this became progressively more impressive proximally so that in the descending colon there were extensive areas of shallow ulceration with erythematous irregular margins and skip areas. This involved the distal transverse colon and seemed to "peter out" in the mid-transverse colon where there were areas of simply of erosion and erythema and the proximal transverse colon appeared normal.	11/02/99 • Mucosal changes were noted from the descending colon to the distal transverse colon. • Patchy areas of edematous hyperemia adjacent to more pale areas. • Frequent diverticular orifices were noted in the sigmoid colon. • The differential diagnosis for the colonic inflammation includes IC

	MAIN BIOPSY FINDINGS			
	07/23/96 • Regular and well ordered crypt architecture • Lamina propria contains the expected component of chronic inflam. cells • Small numbers of neutrophils within the lamina propria • Significant eosinophilic or granulomatous inflammation is not seen. • The subepithelial collagen table is not diffusely thickened • No evidence of a diffuse intraepithelial lymphocytosis. • Mild edema of the lamina propria along with focal fresh hemorrhage. → Diagnostic features of ISCHEMIC-MEDIATED, mucosal injury are not identified.	02/14/98 • The specimen consisted of 5 to 6 fragments, half of which were ischemic. • There was near full thickness ischemia of the mucosa in three of the fragments. → Final pathological diagnosis: ISCHEMIC COLITIS	09/08/98 • Biopsies were most consistent with ISCHEMIC COLITIS with coagulative necrosis that was superficial and inflammatory destruction of superficial crypts with normal architecture and spacing of the deeper crypts and no granulomas.	11/02/99 • The colonic biopsies were interpreted as ISCHEMIC COLITIS (unrelated to test medication, according to the investigator)

The endoscopic evaluations invariably confirm the initial clinical impression as they are consistent with ischemic mucosal type injury, with varying degrees of severity. The patients, who had been hospitalized because of the AE, were discharged with the following diagnosis that included ISCHEMIC COLITIS before results of histopathological examinations were available:

The 1996 patient: Probable ischemic colitis
The 1998a patient: Abdominal pain with hematochezia secondary to ischemic colitis
The 1998b patient: LLQ pain and rectal bleeding secondary to apparent ischemic colitis
The 1999 patient: ISCHEMIC COLITIS

According to this information, all four patients had clinical/endoscopically proven ischemic colitis. The subsequent question is whether the clinical/endoscopic diagnosis of ischemic colitis can be **confirmed** by the pathologist's evaluation of the biopsies taken during endoscopy. The results are not surprising; it is well known that, in some instances, the histopathological evaluation does not confirm the clinical/endoscopic diagnosis. The reasons for this are unknown but may include ascertainment bias and, most important, the fact that the histological features of ischemic vs other colitis are difficult to distinguish. Also, it is worth noting the differential diagnosis considered (see below). This reviewer wishes to emphasize that, whatever post hoc information from histopathologic evaluations may be obtained and added (Dr. Washington et al's imput), this does not negate the fact that clinically (and **this is the most important diagnosis**) these patients **all had ischemic colitis** as the main and most relevant component to explain the clinical picture. In summary (Table 15) the biopsies provided the information highlighted below.

i) The histopathological examination did not identify diagnostic features of ischemic-mediated mucosal injury in the 1996 patient.

ii) In the 1998a patient, the final pathological diagnosis was ischemic colitis.

iii) Biopsies were most consistent with ischemic colitis with concomitant coagulative necrosis in the 1988b patient

and

iv) The colonic biopsies were interpreted as ischemic colitis in the 1999 patient.

Thus, according to these facts, only in the 1996 patient there is a disconnect between the biopsy results and the clinical/ endoscopic diagnosis. In the other three cases, the biopsy data confirmed the clinical/endoscopic impression. Again, one cannot conclude that the cases of ischemic colitis were induced by alosetron.

Etiologically, the available information cannot negate that this IC may co-exist with some other form of colitis or that it may be due primarily or secondarily to some effect of the drug, in association with colitis of infectious origin. In other words, Dr. Washington's evaluations need to be put in the proper perspective.

In the sponsor's November 12, 1999 submission a Section entitled Ischemic Colitis Narrative, explains that Dr. Washington, and an independent reviewer, Dr. Lawrence Brandt, had reviewed the four cases of ischemic colitis occuring in 12-week studies with alosetron. Specifically, Dr. Washington performed histopathological evaluation and immunohistochemistry evaluation for E. coli 0157:H7. H&E preparations were available on all four cases and immunohistochemistry evaluation was done on three of the cases (see Table 15). These findings were presented at the November 16, 1999 GI Advisory Committee meeting and can be succinctly summarized as follows (refer to Table 15):

i) No pathology was present for case 2829 (the 1996 case).

ii) Two cases appear to represent infectious colitis with E. coli positivity on one specimen (the other specimen was not available as the hospital laboratory had lost the paraffin block). The statement is made that Dr. Washington will report to the AC identical appearance of H-E on slides from cases 7195 (the 1998a case) and 15687 (the 1988b case).

iii) Only case 34069 (the 1999 case) represented a histologic diagnosis of ischemic colitis.

Drs. Washington and Brandt concluded that there is no evidence to support a causal relationship between alosetron treatment and development of ischemic colitis. Although this reviewer does not entirely disagree with this statement, additional considerations need to be taken into account.

c. Comments on Dr. Washington's Approach

One cannot make a final diagnosis on the basis of histopathological information alone. It must again be noted that, according to the investigator(s)/consultant, who are the persons close to the experimental subjects (the patients experiencing the AEs), these patients all had a clinical/endoscopic diagnosis of ischemic colitis. The issue is: is this clinical/endoscopic diagnosis confirmed by the biopsy data? If not, what alternatives are there? Opportunities and constraints are highlighted below (refer to Table 15).

i) The 1996 case is already controversial, even before Dr. Washington's intervention, because diagnostic features of - upon biopsy examination - ischemic mucosal injury (suggested by the clinical presentation and confirmed on endoscopy) were not identified. Once again, this is an example (of many) where the biopsy findings do not necessarily confirm the clinical/endoscopic diagnosis.

ii) According to Dr. Washington, both the 1998a and 1998b appear to represent infectious colitis. However, neither case appeared to have occurred during an outbreak of E. coli infection. This is very important because physicians must report to public health authorities the occurrence of E. coli epidemics; this was neither done nor suspected. Moreover, in the 2/15/98 stool culture of the 1998a patient, no salmonella, shigella, yersenia, campylobacter or (more important) E. coli 0157 were isolated [a positive stool

culture does establish the definite diagnosis]. In the other patient (the 1998b case), stool culture was apparently done but not reported.

iii) It is also important to mention that Dr. Washington used an experimental, not yet validated procedure. Nonetheless, the main point of disagreement here is that, although histopathologically, ischemic and infectious components may co-exist, the local pathologist's readings of the biopsy specimens from both patients confirmed the diagnosis of ischemic colitis that had been suspected on the basis of clinical and endoscopic findings. As a matter of fact, in patient 1998b discharge summary (dated 9/10/98), Ronald P. Schwarz, M.D. makes the following comments:

". . . There were multiple shallow ulcers in appearance and distribution most consistent with ischemic colitis and Crohn's disease was in the differential. Biopsies, however, were most consistent with ischemic colitis with coagulative necrosis that was superficial and inflammatory destruction of superficial crypts with normal architecture and spacing of the deeper crypts and no granulomas.

"The patient's clinical course was also consistent with ischemic colitis in that she gradually and fairly rapidly improved with lessening of pain and cessation of bleeding. Therefore, no specific therapy was given. She was advanced to a regular diet and discharged. She underwent Doppler ultrasound of her mesenteric vessels to rule out any large vessel problem which was considered unlikely and this result is pending.

"It remains unclear whether her colitis was a side effect or complication of her study drug but this was considered less than likely, however, the patient does not have any obvious risk factors for ischemic colitis otherwise . . ."

iv) According to Dr. Washington, only the 1999 case represented a histologic diagnosis of ischemic colitis. This is in agreement with the pathologist's evaluation of the biopsies which, as pointed out above, confirmed the suspected clinical/endoscopic suspicion of ischemic colitis. However, results of stool culture for E. coli in this patient were not available. Moreover, from the CT scan, infectious inflammatory colitis is considered the most likely [NOTE: Admittedly, this may represent an over-reading of the CT scan]. According to this report, ischemic colitis was felt to be unlikely given the involvement of multiple vascular territories (inferior mesenteric artery=IMA and superior mesenteric artery=SMA, Table 15). It is said, however, that IC cannot be completely excluded on the basis of the CT scan examination.

v) It is of interest to bring out the issue of differential diagnoses considered in each case (Table 15):

1996 case:	"Less likely infectious vs IBD"
1998a case:	"Secondary causes for ischemic colitis will likely need to be evaluated"
1998b case:	"Crohn's disease or self-limiting colitis"
1999 case:	"Infectious or inflammatory is considered the most likely; ischemic colitis cannot be completely excluded"

Incidentally, it is not surprising for conditions such as Crohn's disease to be included in the differential diagnosis. This is because the modern approach to IBS, both clinically and during experimental trials in humans, emphasizes diagnosing the condition primarily on the basis of compatible signs and symptoms while depending less and less in the use of diagnostic devices. So, using this modern approach, some patients with organic disease of the gut may be misdiagnosed as having IBS. An example is patient #4595, in principal Phase III Study S3BA3001. This is the patient that experienced transaminitis and mild elevation of bilirubin [reviewed under V. B. 2.f) above]. Following four weeks of ALOS treatment, this patient experienced rectal bleeding (3/30/98 through 4/1/98). On endoscopy, Crohn's disease was diagnosed which, as of 4/17/98 had not resolved. The most likely possibility is that this patient had already Crohn's disease at the time of randomization into the trial.

vi) The reviewer's conclusion is that all four patients being considered had a clinical syndrome of ischemic colitis that was confirmed on endoscopy but not always supported by histopathological findings. This schemic colitis may coexist or even be the consequence of some form of E. coli infection. This infection is somewhat common. Marshall and his coworkers[38] from the Mayo Clinic, now routinely culture stool specimens for this organism. To determine the prevalence of E. coli 0157:H7-associated diarrhea in their patient population, they surveyed all submitted stool cultures for 6 months for this organism. Specimens were screened for non-sorbitol fermenting E. coli and confirmed by slide-agglutination and immobilization testing. Of 2,164 specimens, 10 yielded E. coli 0157:H7 by this approach [NOTE: This incidence seems similar to the one reported in the alosetron trials considered here]. It was the fourth most common bacterial stool pathogen found. These authors concluded that E. coli 0157:H7 causes sporadic infections in the Mayo Clinic patient population and should be considered in the differential diagnosis of acute hemorrhagic colitis.

vii) The MTL believes that there is no clear cut evidence for a causal relationship between alosetron treatment and the development of this colitis, which appears to be acute and possibly self-limiting. On the other hand, the direct or indirect contribution of alosetron use to this complex clinical/endoscopic/histopathological picture cannot be completely rule out. It is true that, as far as we know, all cases resolved without sequelae and there were no instances of necrosis/perforation that may necessitate colectomy.

One important reason not to entirely exonerate alosetron is that these four cases of ischemic colitis occurred exclusively among women that were taking the drug and none among the patients taking placebo. This is a hard to explain/accept coincidence. This reviewer agrees with Dr. Senior's recommendation that "if alosetron is approved for marketing, a prospective study of a sufficient cohort of patients starting treatment with alosetron should be observed on treatment to detect and investigate cases of rectal bleeding, to improve our estimate of its true incidence, obtain information on risk factors, and other useful information pertinent to ischemic colitis [see separate memorandum by the MTL and the Division's Director on this matter]. The study should be designed to be

[38] [W.F. Marshall et al. Results of a 6-month survey of stool cultures for Escherichia coli 0157:H7. Mayo Clinic Proc. 65:787-792 (1990)]