Inflammatory Bowel Disease

- Questions -

1. Which one of the following characteristics of the gastrointestinal (GI) mucosal immune system is false?

The mucosal immune system involves:

A. Production of antibodies of all 5 immunoglobulin classes (IgM, IgG, IgA, IgD, IgE).

B. Cell-mediated immunologic responses, including natural as well as antibody-dependent cytotoxicity.

C. Export of immunoreactive cells to many other mucosal areas and to systemic lymphoid sites.

D. Delayed-type hypersensitivity reactions which does not involve CD4 positive nor CD8 positive cells.

E. Suppression of many systemic immunologic responses (tolerance).

The recommended response is D.

The mucosal immune system is a large multiorgan system that involves production of antibodies of all 5 immunoglobulin classes (IgM, IgG, IgA, IgD, IgE). It involves cell-mediated immunologic responses, including natural as well as antibody-dependent cytotoxicity. Also, it involves export of immunoreactive cells to many other mucosal areas and to systemic lymphoid sites. It
involves suppression of many systemic immunologic responses (tolerance). It involves immediate type-hypersensitivity and it can involve delayed-type hypersensitivity reactions. The Type IV or delayed type hypersensitivity takes two to three days to develop and involves a CD4 or CD8 cell mediated response.


2. Which statement about humoral immunity in inflammatory bowel disease (IBD) is false? :

A. In IBD, B lymphocytes function in a classic manner serving two principal and related functions: antibody production and presentation of antigen to T lymphocytes.

B. An increase in IgG production by lamina propria mononuclear cells in patients with IBD has been well described compared to healthy controls and patients with acute infectious colitis.

C. The presence and the titer of p-ANCA is known not to correlate with disease activity or medical therapy or to change after colectomy.

D. In vitro, peripheral blood mononuclear cells from patients with IBD and other autoimmune disorders, such as systemic lupus erythematosus and Henoch-Schonlein purpura have an elevated spontaneous production of IgG, IgA, and IgM compared to healthy controls.

E. The p-ANCA does not occur in patients with Crohn’s disease (CD)
and, thus, serves as an excellent way to serologically differentiate ulcerative colitis (UC) from CD.

The recommended response is E.

In IBD, B lymphocytes function in 2 ways, including antibody production and presentation of antigen to T lymphocytes. An increase in IgG production by lamina propria mononuclear cells in patients with IBD is well documented when compared to healthy controls and to patients with acute infectious colitis. The increase in IgG production is found to be a finding in patients with either UC or CD. Ulcerative colitis is associated with increased production of IgG₁ and IgG₃, whereas CD is associated with increased production of IgG₂. IgG₁ and IgG₃ antibodies account for the predominant IgG response to proteins and T-cell-dependent antigens. IgG₂ provides the predominant IgG response to carbohydrates and many bacterial antigens. Delineation of the stimuli and antigens that induce the increased secretion of IgG subclasses may provide insight into the etiology and pathogenesis of IBD.

It has also been well documented that in vitro, peripheral blood mononuclear cells from patients with IBD and other autoimmune disorders, such as systemic lupus erythematosus and Henoch-Schonlein purpura, have an elevated spontaneous production of
IgG, IgA, and IgM compared to healthy controls.

Finally, the p-ANCA does occur in patients with CD and, thus, does not serve as an excellent way to serologically differentiate UC from CD.


3. Which one of the following statements about Ulcerative Colitis is true?

A. The presence of an inflammatory infiltrate of neutrophils, lymphocytes, plasma cells, and macrophages is found in the colon; not in the small bowel.

B. The plasma cells invade the epithelium, usually in the crypts, giving rise to cryptitis and ultimately to crypt abscesses.

C. Histologically, goblet cell excess is commonly seen in colonic mucosa of patients with active UC.

D. A marked increase in lamina propria plasma cells occurs, with the majority of these being IgM-containing cells and a smaller percentage being IgG-containing cells.

E. Crypt architectural distortion is prototypically absent in patients with active UC but is more frequently encountered in patients with Crohn’s Disease who have active colonic disease.

The recommended response is A.

In the colon of patients with UC there is a chronic inflammatory infiltrate with the
presence of neutrophils, lymphocytes, plasma cells and macrophages. This inflammation does not extend to the small bowel. The small bowel of patients with UC remains unaffected. In the colon, cryptitis is associated with discharge of mucous from goblet cells and increased epithelial cell turnover. Histologically, this results in the appearance of goblet cell depletion, and the cells become more basophilic, an indicator of young, immature cells. In UC, a marked increase in lamina propria plasma cells occurs with the majority of these being IgG-containing cells and a smaller percentage being IgM-containing cells. The presence of crypt architecture distortion is a feature that is characteristically present in patients with UC not necessarily in patients with CD. This microscopic finding is important since this finding is absent in patients who have acute self-limited colitis. It indicated chronicity and is not specific for IBD; but can be observed in chronic conditions such as colonic ischemia.

4. Which one of the following accurately (i.e., is true) reflects the epidemiologic features of IBD?

A. The prevalence and incidence of UC is more common in Asian Americans than in Caucasians.

B. Ulcerative colitis has increased in incidence and prevalence at twice the rate of CD.

C. In general, there is a higher prevalence of IBD in the southern parts of North America and Europe than in the northern parts.

D. North American males are more likely to develop UC than North American Females.

E. Jews who were born in North America or who migrated to Israel are at a higher risk of UC than those born in Israel, who are themselves at a higher risk than those born in Africa or Asia.

The recommended response is E.

The prevalence of both UC and CD is at least 100 patients per 100,000 general population. Thus, in the United States, the total number of patients with IBD is at least 500,000 people, perhaps more. Men and women in North America are equally as likely to develop
inflammatory bowel disease (either CD or UC). Inflammatory bowel disease spares no socioeconomic class. Jews of Ashkenazi descent are 2- to 3-fold more likely to develop IBD, particularly CD, than non-Jews. The country of birth of a person plays a role in the risk of developing inflammatory bowel disease. Jews who were born in North America or who migrated to Israel are at a higher risk of UC than those born in Israel, who are themselves at a higher risk than those born in Africa or Asia. It has been suggested that there is a higher prevalence of IBD in the northern parts of North America and Europe than in the southern parts. Finally, people who smoke are more likely to get CD and less likely to get UC.


5. A 25-year-old woman with a 2-month history of UC presents to the emergency department with fatigue, abdominal pain, hematochezia and diarrhea. Since the time of her initial diagnosis with UC she has been treated with prednisone 40 mg daily and
Mesalamine 4 grams daily. For the last week she has had approximately 10 bowel movements daily and cramping abdominal pain. She is admitted to the hospital, where hydration and parenteral corticosteroids are given. Over the ensuing 12 hours, (approximately 18 hours after admission) her abdominal pain becomes worse, she develops abdominal distension and obstipation. On physical examination she has a temperature of 38.6°C, her pulse rate is 120/minute, and her abdomen is distended and diffusely tender with rebound. She had an abdominal flat plate radiograph that demonstrated a dilated transverse colon to 8 cm with thumb-printing. No free intraperitoneal air was observed. At this point in time, the most appropriate therapy for this patient is:

A. Oral and topical high-dose Mesalamine.
B. Intravenous cyclosporine.
C. Intravenous 6-mercaptopurine or azathioprine
D. Intravenous infliximab
E. Urgent subtotal colectomy.

The recommended response is E.

Acute toxic megacolon is estimated to occur in 6% to 13% of patients with UC. When toxic megacolon is treated in a prompt fashion, subsequent surgery is not inevitable. In patients who have prompt resolution of the megacolon, approximately half require surgery within a year and most eventually require colectomy. In the
presence of acute toxic megacolon caused by UC, surgery can be associated with significant morbidity and mortality. Postoperative complications (sepsis, wound infections, abscess, fistula, and delayed wound healing) have occurred in up to 50% of patients. Postoperative mortality ranges from 11% to 16% and for the subset of patients with perforation, 27% to 44%. The mortality rate is 8.7% and 6.1% after total abdominal colectomy and 14.7% for total proctocolectomy. This observation suggests that a more conservative surgery is appropriate in the acute setting. With the popularity of anal sphincter-sparing procedures, one should always weigh the possibility of later surgery for restoration of continence. In particular, leaving the rectum intact allows its use for subsequent mucosal proctectomy and ileoanal anastomosis.

Intravenous corticosteroids, intravenous infliximab and intravenous cyclosporine are effective therapies for severely active UC, but have not been proven in patients with toxic megacolon. 6-mercaptopurine has a delayed onset of action for 3 to 6 months and is not indicated for toxic megacolon. Methotrexate has been shown to be effective for CD and Mesalamine is only effective for mild to moderately active UC.


6. Which one of the following endoscopic features is most typical for UC?

A. Serpiginous Ulcerations
B. Aphthous ulcerations.
C. Pseudopolyps
D. Deep ulcerations or fissures.
E. Colonic stricturing.

The recommended response is C.

Pseudopolyps are typically found in patients with UC, not in patients with CD. The creeping fat observed in patients with CD is an extension of mesenteric fat and, thus, originates on the mesenteric border.
Additional typical radiologic features of CD include deep linear ulcers, superficial or aphthous ulcers overlying lymphoid follicles. The presence of fistulae should signal the presence of CD. Fistulae usually burrow through adjacent organs when present; hence the presence of rectovaginal fistula, ileovesicular or colovesicular fistulae is not infrequent in those patients with active disease. Patients with CD may have skip areas, and in some patients, strictures. Strictures are not classically seen in UC. When strictures are observed in patients with UC, the clinician should have a heightened alert for the potential coexistence of a colorectal carcinoma.


7. As a senior medical resident you are asked to admit a 28-year-old woman who carries a diagnosis of UC. She has documented continuous disease from the anal verge to 20 cm from the anal verge. Which one of the following serological
combinations best describes the finding(s) that is (are) likely to be found in association with the diagnosis of distal UC in this patient?

A. Positive pericytoplasmic Anti-Neutrophil Cytoplasmic Antibody (p-ANCA).
B. Positive Anti-Saccharomyces Antibody IgG and IgA.
C. Antibodies against OmpC.
D. Antibodies against I2.
E. Antibodies against CBir1

The recommended response is A.

The use of serologic tests in patients with IBD detect the presence of antibodies against self or non-self proteins. The most extensively evaluated serologic markers in IBD include perinuclear p-ANCA and Anti-Saccharomyces Cerevisiae (ASCA). These serologic immune markers have been used by many physicians in an attempt to diagnose and to differentiate amongst the various forms of IBD (i.e., CD from UC).

p-ANCA is detected in the serum in 60% to 70% of patients with UC and in 10% to 20% of patients with CD. ASCA is present in 50% to 70% of patients with CD in 6% to 14% of patients with UC. ASCA is rarely expressed in patients who do not have IBD and, thus, is believed to be rather specific for patients who have CD. Patients with CD who express both IgG and IgA ASCA, the so called “double ASCA
positive,” are more likely to have fibrostenosing and internal penetrating disease behavior when compared to p-ANCA positive/ASCAnegative CD patients. In the latter group of patients with CD, their disease likely resembles UC in terms of clinical presentation and endoscopic findings and are also referred to as “UC-like CD.”

These serologic tests have also been used by gastroenterologists as screening tools in the initial evaluation of patients with symptoms suggestive of IBD, particularly in the pediatric population where the use of radiologic studies is typically minimized. In children referred to a specialty IBD clinic for evaluation of nonspecific GI complaints, 95% of non-IBD patients were negative for p-ANCA and ASCA, and as per the authors, could have avoided further testing. Patients who have persistent symptoms or with a high likelihood of having IBD deserve further investigation, even in the face of negative serologies. Recently, several other newer serologies have been added, such as the detection of antibodies against OmpC (a bacterial porin protein from Escherichia Coli) and I2 (a novel bacterial superantigen), both associated with CD. Positive serologies usually warrant confirmatory tests.

In a recent study Anti-flagellin (anti-Cbir1) antibody and Crohn’s disease (CD) were reported to be associated in 303 CD patients: Anti-Cbir1 was detected in 51%, Anti-I2: 59%, Anti-ompc 46%, ASCA 52%. Anti-Cbir1 had 61% association with complicated Crohn’s disease versus 42% with inflammatory disease only. There was a positive association with fistulizing, fibrostenotic small bowel disease irrespective of
other markers. CBir1 was discovered to to associated with small bowel and complicated disease. The presence of this antibody was most correlated with fibrostenosis and internal perforating disease (Targan SR, Landers CJ, Yang H, Lodes MJ, Cong Y, Papadakis KA, Vasiliauskas E, Elson CO, Hershberg RM. Antibodies to CBir1 flagellin define a unique response that is associated independently with complicated Crohn's disease. Gastroenterology. 2005 Jun; 128(7):2020-8.) It is important to point out that Bacterial flagellin, a subunit of flagella, has been identified as a dominant antigen in Crohn’s disease by activating toll like receptor-5, one of several toll like receptors that are effectors of the innate immune response.


8. Some of the following extraintestinal manifestations of IBD typically parallel the course of clinical disease activity and others do not improve in parallel with improvement in intestinal symptoms. Which one of the following statements is false?

A. Peripheral arthritis is the most common extraintestinal manifestation in patients, occurring in 5% to 20% of individuals. The risk increases as the extent of colonic involvement increases.

B. Uveitis usually manifests as an acute or subacute painful eye with
visual blurring, photophobia, headache, and iridospasm. The
temporal relationship of uveitis with bowel disease activity is very
predictable. Uveitis classically parallels bowel activity.

C. Sacroiliitis may be isolated and asymptomatic. Sacroiliac joint
changes can often be present on magnetic resonance imaging
(MRI). Most patients with sacroiliitis are HLA-B27 negative and
do not progress to ankylosing spondylitis

D. Episcleritis -- characterized by painless hyperemia of the sclera and
conjunctiva with loss of vision. This parallels the disease activity.

E. Pyoderma gangrenosum occurs in 1% to 4% of patients with IBD
and seems to be more common in patients with UC than CD. Four
distinct variants exist – the pustular type, the bullous or atypical
pyoderma, the ulcerative type, and the vegetative type. The
vegetative type is the most common type and is the classic subtype
seen in patients with IBD.

The recommended response is B.

Peripheral arthritis, erythema nodosum, aphthous ulcers, and episcleritis
all tend to run a clinical course that parallels the activity of the
patient’s underlying IBD. Medical and surgical therapies directed
toward inducing remission of the patient’s IBD are likely to be
successful and bring the extraintestinal manifestations under
control. In contrast, amyloidosis, ankylosing spondylitis, sacroiliitis,
and pyoderma gangrenosum tend to run a clinical course which is independent of the patient’s underlying IBD, and medical therapies directed specifically toward these extraintestinal manifestations may be required. Peripheral arthritis is the most common extraintestinal manifestation in patients, occurring in 5% to 20% of individuals. The risk increases with the extent of colonic involvement and with complications such as abscesses, perianal disease, erythema nodosum, stomatitis, and pyoderma gangrenosum.

Uveitis usually manifests as an acute or subacute painful eye with visual blurring, photophobia, headache and iridospasm. The temporal relationship of uveitis with bowel disease activity is not very predictable. Sacroiliitis may be isolated and asymptomatic. Sacroiliac joint changes are often present on MRI. Most patients with sacroiliitis are HLA-B27 negative and do not progress to ankylosing spondylitis. Episcleritis is characterized by painless hyperemia of the sclera and conjunctiva with loss of vision. This parallels the disease activity. Pyoderma gangrenosum occurs in 1% to 4% of patients with IBD and seems to be more common in patients with UC than CD. Four distinct variants exist: the pustular type, the bullous or atypical Pyoderma, the ulcerative type, and the vegetative type. The ulcerative type is the most common type and is the classic subtype seen in patients with IBD.


9. All of the following complications are known to occur as a consequence of CD except (choose 1):

A. Fecaluria (as a manifestation of Fistula formation to the bladder from adjacent loops of bowel).

B. Perianal abscess formation.

C. Colonic stricture formation with subsequent large bowel obstruction.

D. Development of renal dysfunction as a manifestation of secondary amyloidosis
E. Development of left-sided hydrourerter

The recommended response is E.

The transmural inflammatory process of CD predisposes to the formation of fistulae. The presence of fistulae signifies that the transmural inflammation has penetrated into adjacent organs, tissue, or skin. The classification of fistulae is based upon their location and their connection with contiguous organs. In the literature, fistulae have been described as either: 1) internal if they terminate into adjacent organs (e.g., enteroenteric, enterovesical, ileocolic, gastrocolic, rectovaginal) or into the nearby mesentery, or 2) external if they terminate on the surface of the patient's body (e.g., enterocutaneous, parastomal, perianal). It is not uncommon that the transmural inflammation that is present in CD evolves into a fistula. A fistula may subsequently have feces and associated bacteria leave the intestinal lumen and lead to the formation of an abscess. Additionally, a fistula may develop between the bowel (typically the sigmoid colon or terminal ileum-based on anatomic proximity) and the bladder. A patient may develop pneumaturia (air in the urine) or Fecaluria (stool in the urine) with recurrent cystitis. The infections that results are usually polymicrobial in origin. The lifetime risk for the development of a fistula in patients with CD has been reported to typically range from 20% to 40%; though in some series their presence has varied from as low as 17% to as high
as 85%

Individuals with Crohn’s disease may develop inflammation of the ileum and/or cecal region with an associated phlegmon. A phlegmon presents as a poorly-defined mass of soft tissue density with increased attenuation when evaluated by computed tomography in adjacent fat and ill-defined soft tissue planes. The inflammation leads to localized pressure and obstruction of the ureter on the right where the ileum and the ureter cross anatomically. This classically does not occur on the left side.

Secondary amyloidosis may develop in individuals with longstanding Crohn’s disease. The most common cause of morbidity associated with amyloidosis is renal failure and dysfunction. Colectomy or surgical intervention does not influence the course of disease.


10. Joann, a 24- year-old female postal worker has had UC since childhood involving her entire colon (pancolitis). She presents to you for evaluation of his risk for development of colorectal carcinoma. She has recently read something in the internet and is unsure of its validity. She requests that you discuss factors with her that are known to increase the risk of a patient with ulcerative colitis for the development of colorectal carcinoma.

All of the following are independent risk factors for the development of colorectal cancer in this patient with UC except:
A. Extent of colonic involvement

B. The severity of disease at initial presentation

C. The presence of low-grade dysplasia on biopsy of the mucosa.

D. A family history of colon cancer in a first-degree relative.

E. The concomitant presence of primary sclerosing cholangitis.

The recommended response is B.

Patients with extensive or pancolonic UC are at greater risk for developing cancer than patients with left-sided or distal UC. Patients with ulcerative proctitis have a risk that is similar to the general population. A disease duration of greater than 10 years for pancolitis is associated with an increased risk of colorectal cancer, whereas for patients with left-sided or distal UC, the risk probably does not increase until 15 to 20 years' duration. Patients whose age at onset is at 14 years of age may be at an especially increased risk for developing cancer in the setting of UC. Older age of onset (>60 years) is not an independent risk factor. Recently, studies have shown that a family history of colorectal cancer and the concomitant presence of primary sclerosing cholangitis are also independent risk factors for developing colorectal cancer in the setting of UC.

Dysplasia is believed to be a precursor lesion in the pathway towards the development of invasive carcinoma in patients with UC. Since 1983, dysplasia has been categorized according to the recommendations of the Inflammatory Bowel Disease Morphology Study Group. This group recommended that biopsy specimens
be classified as negative for dysplasia, indefinite for dysplasia, low-grade dysplasia, and high-grade dysplasia. When dysplasia is identified in macroscopically abnormal mucosa it is classified as a dysplasia-associated lesion or mass (DALM).

Guidelines for cancer surveillance in UC have attempted to base recommendations on the predictive value of the findings of low-grade and high-grade dysplasia for the concurrent or subsequent development of cancer. Bernstein et al. performed a systematic review of the medical literature and reported that 32% of patients who developed high-grade dysplasia after an initially normal colonoscopy were subsequently found to develop cancer. Similarly, 33% of patients with high-grade dysplasia on the initial colonoscopy were eventually diagnosed with cancer. In patients with newly diagnosed low-grade dysplasia on colonoscopy after a previously normal surveillance colonoscopy, 16% progressed to high-grade dysplasia, DALM, or cancer (8%). In patients with low-grade dysplasia diagnose at the first surveillance colonoscopy, 29% progressed to high-grade dysplasia, DALM lesion, or cancer (13%). The importance of DALM was highlighted in a study by Blackstone et al. Twelve patients were identified with DALM lesions during surveillance colonoscopies, of whom 7 (58%) were subsequently found to have cancer. Thus, the presence of a DALM lesion or high-grade dysplasia appears to be highly predictive of the presence of concurrent cancer or the future development of such. Similarly, patients with low-grade dysplasia would appear to be at relatively high risk of developing high-grade dysplasia or cancer, and some may have concurrent cancer. The predictive value of low grade dysplasia remains controversial as other investigators have reported much lower frequencies of progression to high-grade
dysplasia or carcinoma.

Some patients will develop cancer despite recent negative surveillance colonoscopies. Woolrich et al., reported the discovery of unsuspected colorectal cancer in 1 of 3 patients who underwent colectomy for intractable disease after negative surveillance biopsies. Failure to identify dysplasia during surveillance biopsies may result from sampling errors as biopsies sample only a small fraction of the total mucosa. Studies of colectomy specimens suggest that 56 jumbo biopsies are needed to have 95% confidence of detection of dysplasia if it is present, 64 biopsies to detect cancer if present, and a minimum of 18 biopsies to detect either cancer or dysplasia if present.

The severity of disease at initial presentation has not been associated with subsequent risk for the development of colorectal carcinoma. This has, however, been associated with the subsequent risk for requiring a colectomy due to disease activity.


11. The following histological and endoscopic findings are found in a patient with a history of UC when undergoing surveillance colonoscopy. Colectomy is not indicated in 4 of these patients. Which patient does need referral for colectomy?

A. A 45-year-old man with no dysplasia from flat mucosa involved with UC involving his entire colon (pancolitis) in multiple separate foci. The colitis was inactive at the time of colonoscopic biopsy. The duration of colitis is 20 years.

B. A 52-year-old woman with a 7 mm sessile adenomatous polyp from the right colon. The patient is known to have left-sided UC of 10 years' duration. No other foci of dysplasia were identified.

C. A 30-year-old woman with a sessile 5mm hyperplastic polyp in the rectum with indefinite low-grade dysplasia in the sigmoid colon in one focus. The patient is known to have left-sided UC. The disease was inactive at the time of colonoscopy and insignificant inflammation was noted to be present in the biopsies.

D. A 50-year-old man who had no dysplasia from flat mucosa in a recent colonoscopy. The patient has pancolonic UC and 6 months earlier had biopsies of the sigmoid and descending colon that showed definite low-grade dysplasia in 3 separate foci. No active
inflammation was present at that time. At the time of this colonoscopy the disease was inactive with virtually no inflammation on biopsy.

E A 47-year-old woman who has colitis to the midtransverse colon that is currently inactive. A 1.5 cm pedunculated polyp in the sigmoid colon was excised by snare electrocautery and was found to be an adenoma. The margins were clear and the polyp was excised in its entirety. Biopsy of the base of the polyp (i.e., the surrounding mucosa) demonstrated no dysplasia in the flat mucosa (of a total of 12 biopsies obtained in that area).

The recommended response is D.

Patients who have definite low-grade dysplasia from flat mucosa involved with UC who are undergoing surveillance colonoscopy have a significant risk of developing cancer during follow-up and should undergo colectomy. Patients with left-sided UC with an adenomatous polyp in the right colon with surrounding mucosa uninvolved with UC can be treated as having a sporadic adenomatous polyp and undergo endoscopic polypectomy. Patients with a dysplastic polyp arising in the setting of UC should be considered to have a DALM lesion; they have a 50% risk of having a cancer within the lesion and should undergo colectomy. Patients who have dysplasia identified in flat mucosa should undergo colectomy. If they have a subsequent colonoscopy that does not detect dysplasia colectomy should still be performed in
order to be safe. It is likely that the area is missed despite multiple biopsies. It should be noted that hyperplastic polyps do not carry an increased risk for the development of colorectal carcinoma. Patients of the correct age (i.e., those at risk for adenomas – age approximately 50 or older) who have dysplastic polyps (adenomas) in the area of colitis (in the absence of high-grade dysplasia and when lesions do not have malignant endoscopic appearances) should be considered to have sporadic adenomas. These patients need to have the mucosa surrounding the polyp biopsied in order to ensure the absence of a field defect with surrounding dysplasia in the mucosa. Patients with dysplasia in the mucosa surrounding a pedunculated or sessile colonic polyp should undergo colectomy. They are believed to have a field defect in the colon and this is a perceived manifestation of multifocal dysplasia.


12. In discussing the potential for complications with a colorectal surgeon,
a 30-year-old Caucasian female marathon runner asks questions regarding her prognosis with UC. She is informed of “numerous specific detail” but loses her notepad after she leaves his office and does not recall many specifics. In an attempt to “refresh her memory”, she visits a “University” web site. Several statements are made in the forum of a chat room by another “educated” patient regarding surgery in UC. Which one of the following statements made by other patients regarding surgery for UC is true?

A. Fertility is decreased in patients who undergo a total proctocolectomy and creation of an ileoanal J pouch.

B. Fecal incontinence is exceptionally rare occurring in less than one in 500 patients and is unlikely to occur in patients after total proctocolectomy with ileoanal J pouch creation.

C. Individuals who have dysplasia or cancer in their sigmoid colon prior to colectomy should not undergo surgery with an ileoanal pouch given the exceptionally high risk for development colorectal carcinoma in the rectal “cuff” of the pouch. The only appropriate option for these patients is a Brooke’s (end) ileostomy.

D. The patients who have a total proctocolectomy with an ileoanal J pouch anastomosis rarely have a postoperative bowel movement maximal frequency of only 1 to 2 bowel movements daily.
E. First-line medical therapy for acute pouchitis in a patient who has had an ileoanal J pouch is typically an immune modulator such as 6-Mercaptopurine or azathioprine or infliximab.

The recommended response is A.

The most common indication for colectomy in the setting of UC is failure of medical therapy to control the patient’s symptoms. Dysplasia and cancer indications would be the second most frequent indication, with other indications such as control of extraintestinal manifestations being very uncommon. Acute pouchitis which readily responds to medical therapy and does not require maintenance suppressive medical therapy occurs in up to 45% of patients over a 10-year follow-up period after creation of an ileoanal pouch or Kock pouch. Chronic pouchitis is relatively infrequent, occurring in only 5% to 7% of patients over 10 years of postoperative follow-up. The first-line therapy for pouchitis is an antibiotic such as metronidazole or Ciprofloxacin. Sulfasalazine and mesalamine products may be tried in patients who fail to respond to antibiotics. Corticosteroids are not generally used for the treatment of pouchitis. Immune modulators (such as 6-mercaptopurine, azathioprine or infliximab) are rarely indicated for the treatment of pouchitis. When a diagnosis of UC versus CD is uncertain, a 3-stage operation is frequently performed. Individuals who have either cancer or dysplasia may undergo treatment with an ileoanal pouch operation. There have been only approximately 15 reported cases of carcinoma of the rectum thus far. The patients who have a total proctocolectomy with an ileoanal J pouch anastomosis
rarely have a maximal postoperative bowel movement frequency of 1 to 2 bowel movements daily; rather the typical frequency is 5 to 8 bowel movements daily.

A recent meta-analysis has assessed complications after ileoanal J pouch surgery and has assessed a total of 43 observational studies comprising a total of 9,317 patients in the literature to develop frequencies of occurrence. (Reference: Hueting WE, Buskens E, Ingeborg VDT, Gooszena HG, van Laarhoven CJHM. Results and Complications after Ileal Pouch Anal Anastomosis: A Meta-Analysis of 43 Observational Studies Comprising 9,317 Patients. Digestive Surgery 2005; 22: 69-79). The initial search based on 1,206 abstracts yielded 43 studies eligible for further analysis. Indications for IPAA were UC in 87.5%, Familial Adenomatous Polyposis Coli in 8.9% and other diagnoses in 3.6%. The median follow-up was 36.7 months. Pouch failure was 6.8%, increasing to 8.5% in case of follow-up of more than 60 months. Pelvic sepsis occurred in 9.5%. Severe incontinence, mild incontinence and urge fecal incontinence were reported in 3.7, 17, and 7.3%, respectively. No effect of experience, duration of follow-up and type of surgical technique on the incidence of pouch failure and pelvic sepsis was demonstrable. The authors thus concluded that current techniques for restorative surgery after proctocolectomy are associated with non-negligible complication rates and leave room for improvement and continuation of development of alternative procedures.

There have been several observational studies that have demonstrated a substantial decrease in fertility for women after undergoing total proctocolectomy with an ileal pouch anal anastomosis (IPAA) for ulcerative colitis.

The following series (by Olsen KO, et al. Gastroenterology. 2002;122:15-19) exemplifies several other observational studies that have demonstrated decreased
cumulative incidence of pregnancies in women undergoing IPAA.

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* P<0.001 vs controls


13. Which of the following statements is false regarding histologic findings in patient with IBD?

A. In patients with UC, the mucosa may revert to normal after treatment. Biopsy of the mucosa may even be normal with complete absence of microscopic abnormalities.

B. Crypt abscesses can be seen in either patients with CD or UC and are not helpful in establishing which disease is present.

C. The presence of crypt distortion is a histologic finding that helps to
differentiate acute self-limited colitis from UC. This particular finding indicates disease chronicity.

D. The finding of aphthous ulcerations in the colon is a very specific finding indicating the presence of CD.

E. In a patient with UC, the presence of an isolated giant cell or a histiocytic reaction around a ruptured crypt, mimicking granuloma formation can occasionally be seen and does not indicate that this particular patient has Crohn’s disease.

The recommended response is D.

Ulcerative colitis always begins at the anal verge and extends proximally in a continuous fashion for a variable distance in the colon. Occasionally, patients who have recently been treated with corticosteroids, mesalamine enemas, or suppositories may have relative rectal sparing, although biopsies of the rectum should show evidence of quiescent UC in these patients. In contrast, the rectum may or may not be involved in patients with Crohn’s colitis, and rectal sparing should strongly raise the possibility of a diagnosis of CD for the endoscopist. Complete mucosal healing in patients with UC has been well documented to occur. It is important to be able to differentiate acute self-limited colitis from idiopathic UC. The presence of crypt distortion is a histologic finding that helps to differentiate acute self-
limited colitis from UC. Deep serpiginous/linear ulcers or “rake ulcers” are typical of CD, not UC. Follow-up endoscopy after instituting a new medical therapy need only be considered if the patient fails to respond. In a patient with UC, it is not necessary to routinely perform a follow-up endoscopy to document mucosal improvement or healing. It is appropriate however, to consider endoscopic evaluation if a patient does not respond to standard therapy in adequate time, in order to exclude the presence of a complication and determine if the symptoms may be unrelated to the IBD (e.g., the patient may have irritable bowel syndrome). The finding of aphthous ulcerations in the colon is not a very specific finding indicating the presence of CD; rather this can be seen with infectious disorders that mimic CD.

Another area that is somewhat difficult microscopically is when a patient with UC as an isolated lesion that appears like a granuloma. The presence of an isolated giant cell or a histiocytic reaction around a ruptured crypt, mimicking granuloma formation can occasionally be seen and does not indicate that this particular patient has Crohn’s disease. Several other findings help establish the presence of UC in patients such as mucosal ulcerations and erosions, mucin depletion, Paneth-cell metaplasia and diffuse thickening of the muscularis mucosae. Erosions and widespread surface epithelial damage are more common in UC than in CD.
Severe, almost total mucin depletion is another feature that distinguishes UC from CD. Paneth cells in Crypts distal to the ascending colon suggest IBD, usually UC.


14. Which one of the following statements about 5-ASA (mesalamine) compounds is false?

A. Oral 5-ASA (mesalamine) in the uncoated form is mostly absorbed proximal to the colon and thus not readily bioavailable. In order to overcome this
various delivery systems have been developed to permit delivery of mesalamine to the small bowel or colon in various locations.

B. Asacol® is 5-ASA (mesalamine) in a Eudragit-S coating that permits release of contents at a pH above 7.0

C. Pentasa® is 5-ASA (mesalamine) in an ethylcellulose coating that permits time dependent release of mesalamine in the small bowel and in the colon.

D. Sulfasalazine (Azulfidine®) is cleaved to its constituent moieties by the enzyme azo reductase and releases 5-ASA (mesalamine) and sulfapyridine. The major site of 5-ASA release is in the colon.

E. Balsalazide (Colazal®) is comprised of 5-ASA (mesalamine) bonded to a 4-Aminobenzoic Acid compound. The mesalamine is released from balsalazide as a result of cleavage by pancreatic enzymes. The active moiety is subsequently predominantly released into the duodenum and jejunum.

The recommended response is E.

Aminosalicylates (5-ASA Compounds) are the most common drugs prescribed for the treatment and of patients with IBD.

Sulfasalazine, the first aminosalicylate used for IBD, is composed of an agent that has antibacterial activity, sulfapyridine, bound to 5-aminosalicylic acid (5-ASA, mesalamine). In the 1970s, it was discovered that the 5-ASA component of the molecule bears the anti-inflammatory activity while the sulfa moiety functions solely as a carrier ensuring delivery to the colon, where sulfasalazine is
broken down by colonic bacteria into its constituents. This fact, along with the relatively high side-effect profile of sulfasalazine and the ease of proximal absorption (absorbed in the jejunum) of mesalamine if not packaged, led to the creation of sulfa-free aminosalicylates that ensure more distal intestinal delivery of 5-ASA. These include several oral and topical mesalamine preparations, alternative azo-bonded carriers, and 5-ASA dimers (See Table in text section). Mesalamine is the term used in the United States for single molecule 5-aminosalicylic acid (5-ASA) which is available in the United States as tablets (Asacol®), capsules (Pentasa®), and enemas and suppositories (Rowasa®).

Olsalazine (Dipentum®) is a 5-ASA (mesalamine) dimer and is cleaved by the enzyme azo-reductase. There is 98% delivery of mesalamine to the colon. Asacol® is 5-ASA (mesalamine) in a Eudragit-S coating that permits release of contents at a pH above 7. Fifteen to 30% of the mesalamine is delivered to the small bowel. In Europe there is Mesalamine packaged in a different form in Eudragit-L that is released above pH 5.5. Pentasa® is 5-ASA (mesalamine) in an ethylcellulose coating that permits release of mesalamine, such that approximately 50% is able to be delivered to the small bowel. Sulfasalazine (Azulfidine®) is cleaved to its constituent moieties by the enzyme azo reductase and releases 5-
ASA (mesalamine) and sulfapyridine. The mesalamine is predominantly released to the colon intact. Balsalazide (Colazal®) is comprised of 5-ASA (mesalamine) bonded to an amino acid (4-aminobenzoic acid). This compound is metabolized into byproducts 5-ASA and 4-aminobenzoic acid.


15. Which one of the following statements regarding 5-ASA (mesalamine) is true?

   A. Oral Mesalamine is effective for the induction and for the maintenance of remission in patients with CD, who have colonic disease distribution.

   B. Mesalamine is effective topically in the form of suppositories for
ulcerative proctitis and in the form of enemas for left-sided UC for the induction and maintenance of remission.

C. Mesalamine is more effective than placebo for induction of remission in patients who have are maintained on infliximab.

D. Mesalamine has been demonstrated to have efficacy as primary therapy for the treatment of perianal fistulizing CD when active disease is present in the rectum.

E. A combination of topical and oral mesalamine therapy in patients with left sided CD has been demonstrated to be more effective than either mesalamine therapy alone in patients with left-colonic CD.

The recommended response is B.

The mesalamine derivative, Pentasa®, begins release in the duodenum and extends throughout the colon to the rectum. Approximately 50% is released to the small intestine. The mesalamine derivative, Asacol®, is coated with a pH-sensitive polymer (Eudragit-S) that releases in the terminal ileum and cecum (above a pH of 7). Approximately 15% to 30% is released into the small bowel. The mesalamine derivative, olsalazine (Dipentum®), comprises 2, 5-aminosalicylate molecules linked by a diazo bond which is cleaved by bacteria in the colon resulting in release of the active 5-aminosalicylate moieties. Olsalazine is thought to be activated throughout the colon from the cecum to the
rectum. Mesalamine administered as a Canasa® suppository dose form has a maximal extent of delivery of 10 to 20 cm, and does not reach to the left colon or splenic flexure. Mesalamine in the form of a suppository is extremely effective for the induction and maintenance of remission for ulcerative proctitis. In contrast, mesalamine administered as a liquid enema Rowasa® dose form will reach to the left colon and as high as the splenic flexure. Mesalamine in the form of an enema is extremely effective for the induction and maintenance of remission for left-sided UC. Mesalamine administration has been demonstrated to be no more effective than placebo for maintenance of remission to patients with CD who have been induced into remission initially by corticosteroids. In addition the use of mesalamine for induction of remission and for maintenance of remission has not been demonstrated to have substantial benefit over placebo based upon data from two separate meta-analyses. The dose studied in a particular study evaluating this was 4 grams of mesalamine. Mesalamine has not been demonstrated to have any clinical efficacy for patients who have fistulizing CD (it is perceived that this is true even if inflammation is present in the rectum; but this has not been formally assessed in any prospective randomized controlled clinical trial.) . Both oral and topical therapy are effective for the treatment of patients with active UC. A combination of topical and oral mesalamine therapy in patients with left-sided UC has been demonstrated to be more effective than either
mesalamine therapy alone in patients with left-colonic UC. This has not been formally evaluated in patients with left-sided CD.


Thomson ABR and Wild GE. Maintenance of Remission in Patients with Crohn’s Disease. In: Satsangi J, Sutherland LR, Colombel JF, Lofberg R,
16. Which of the following medications have not been demonstrated in randomized controlled clinical trials to be effective for maintenance of remission in patients with UC?

A. Oral 5-ASA (mesalamine) derivatives.
B. Methotrexate
C. Azathioprine (Imuran®) or 6-mercaptopurine (Purinethol®).
D. Topical mesalamine (enemas or suppositories).
E. Infliximab.

The recommended response is B.

Both Asacol® and Pentasa® have been shown to be effective for inducing improvement and remission in patients with active UC and for maintaining remission. Effective doses for Asacol® are 1.6 to 4.8 g per day and the effective dose for Pentasa® is 4 g per day. Sulfasalazine (Azulfidine®) is also effective for inducing improvement and remission and maintaining remission in patients with UC at doses of 2 to 4 g per day. Olsalazine (Dipentum®) is effective at a 1 g dose for maintaining
remission in patients with UC. Controlled trials of olsalazine (Dipentum®) at 2 to 3 g doses have not shown a significant benefit for inducing improvement or remission in patients with active UC, probably because of a dose-dependent ileal secretory diarrhea that can occur in approximately 15% of patients treated with olsalazine, particularly at higher doses. Rectal mesalamine (Rowasa® enemas and Canasa® suppositories) are effective for inducing improvement and remission and maintaining remission in patients with left-sided UC and ulcerative proctitis. Azathioprine (Imuran®) is effective for induction and for maintenance of remission in patients with UC. Corticosteroids are effective agents for induction of remission but not for maintenance of remission. Infliximab has been demonstrated to be effective in clinical trials for both induction of remission or maintenance of remission in patient with UC. Methotrexate has been demonstrated to be ineffective for induction of remission and also has been demonstrated to be ineffective to maintain remission in patients with UC.


American College of Gastroenterology, Practice Parameters
17. Which one of the following statements about methotrexate as it relates to IBD is true?

A. Methotrexate inhibits the enzyme Methylhydrofolate reductase.

B. When given orally at 12.5 mg, Methotrexate is no more effective than placebo for induction of remission in patients with UC.

C. Methotrexate, when administered to a patient, may cause an irreversible often fatal hypersensitivity pneumonitis to develop and require treatment with corticosteroids for its resolution.

D. Methotrexate is safe to administer to women who are pregnant.
when given at a dose of 25 mg intramuscularly every week.

E. Methotrexate is known to inhibit the enzyme Thiopurine Methyl Transferase (Similar to 6-mercaptopurine and azathioprine) in vitro. Deficiency of the enzyme is known to be the cause of hepatic cirrhosis in individuals who receive this medication.

The recommended response is B.

Sulfasalazine, mesalamine, and corticosteroids are safe for use during pregnancy. In retrospective studies, there is no increased risk for birth defects when 6-mercaptopurine and azathioprine are taken at conception or during pregnancy, and it is reasonable to use these medications in selected patients with IBD during pregnancy. Methotrexate has been associated with birth defects and spontaneous abortion and is contraindicated in women who are attempting to conceive or who are pregnant. Methotrexate inhibits the enzyme dihydrofolate reductase. Methotrexate also inhibits the enzyme Thiopurine Methyl Transferase (Similar to 6-mercaptopurine and azathioprine) in vitro. Deficiency of the enzyme is known to be associated with significant bone marrow toxicity. A hypersensitivity pneumonitis may develop in patients (usually easily treated and reversible) who are using methotrexate and requires treatment with corticosteroids for its resolution. Methotrexate has not been shown to
be effective for patients with UC when given at a dose of 12.5 mg orally in uncontrolled trials. Based upon published data from a randomized, placebo-controlled, double-blind trial, when methotrexate is given orally it is no more effective than placebo for patients with UC for the induction of remission.


18. When counseling a patient regarding the risks and benefits of using infliximab, a discussion regarding safety and efficacy is merited. All of the following potential side effects have been directly attributed to the use infliximab and may be encountered except which one of the following?

A. Infections such as sinusitis.

B. Active tuberculosis from reactivation of old tuberculosis.

C. Arthralgias in the presence of a newly positive antinuclear antibody and a newly positive anti-double stranded DNA antibody.

D. Rash, myalgias, and fever occurring 2 to 12 days post-infliximab infusion in a
patient previously exposed to infliximab with a subsequent long hiatus between infusions.

E. Anal squamous cell cancers.

The recommended response is E.

The cytokine, Tumor Necrosis Factor Alpha (TNF-α), is elevated in the bowel mucosa, serum, and stool of patients with active IBD (primarily CD, but also UC). Infliximab is a chimeric monoclonal antibody that is 25% murine and 75% human. Infliximab has a high specificity, affinity, and avidity to TNF-α. Studies of infliximab have illustrated efficacy for moderately to severely active CD and for closing enterocutaneous and perianal fistulas. The optimal dose of infliximab is 5 mg/kg administered as a 2-hour infusion and the clinical effect lasts approximately 8 weeks. Two multicenter studies have suggested that repeated infliximab infusions administered every 8 weeks can maintain remission in patients with treatment-resistant CD. Presently, the data for UC support the routine use of infliximab for this indication—both for induction of remission and for maintenance of remission. Side effects reported with infliximab include infectious complications such as acute sinusitis, reactivation of tuberculosis in those patients previously exposed (which has led to several patient deaths). It is thus suggested that all patients have ppd testing prior to initiation of r therapy with infliximab. In addition, there have been acute infusion reactions, delayed hypersensitivity reactions (myalgias, arthralgias, and fever, frequently 2 to 12 days after infusion), formation of auto-antibodies (ANA and anti-double stranded DNA), leading in rare cases to drug-induced
lupus-like reactions. There have been several patients reported who developed non-Hodgkin’s lymphoma; however, the number of cases observed thus far is consistent with population-based controls. Thus, the use of infliximab can not currently be causally linked with the development of lymphoma; however, this possibility cannot be excluded. Also, the use of infliximab for fistula healing in patients with CD has been quite impressive. No suggestion of any association has been reported for development of anal squamous cell cancer.


19. Several different complications related to medications used to treat patients with IBD may occur. Which of the following adverse event does not match the agent?

A. Mesalamine : Pancreatitis

B. Azathioprine / 6-Mercaptopurine : Pancreatitis
C. Methotrexate: Hypersensitivity Pneumonitis.

D. Cyclosporin A: Seizure

E. Infliximab: Pancreatitis

The recommended response is E.

In general medications used to treat patients with IBD are considered safe; however potential complication may occur. These complications need to be recognized so that appropriate medical intervention may occur. The benefit must be balanced against the potential risk of use of medication. Pancreatitis has been reported to occur with the use of Azathioprine / 6-MP. This reaction typically occurs within the first 3 to 4 weeks and is idiosyncratic. If this reaction occurs with 6-MP then it will likely recur with AZA and vice versa. The occurrence of Pancreatitis does not lead to chronic pancreatic disease. In a similar fashion Pancreatitis can occur with any mesalamine derivative. Methotrexate use can be associated with the development of a hypersensitivity pneumonitis. If recognized early (symptoms typically are dyspnea) then corticosteroids can be initiated which typically leads to complete symptomatic resolution. Seizures have been reported to occur in patients with UC who are taking Cyclosporine for severe ulcerative colitis. Seizures have been described especially in patients with low serum cholesterol.

Infliximab has not classically been associated with the development of Pancreatitis.

Lichtenstein GR, Abreu M, Cohen R and Tremaine W. American Gastroenterological Association Institute Medical Position Statement on Corticosteroids, Immunomodulators,