Colitides

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Abstract. – OBJECTIVE: This Review provides an overview of the pathophysiology, epidemiology, histopathology, clinical characteristics of non-IBD forms of colitis over than some preliminary therapeutic evidences.

STATE OF THE ART: The term "Colitides" includes a variety of inflammatory diseases of the colon. These forms of colitis occur as either primary conditions or complications of other diseases. The etiopathogenesis of most of them remains obscure and the epidemiological data are rather limited. Clinical presentations include chronic, watery diarrhea, abdominal pain and intermittent rectal bleeding. Endoscopic evaluation and mucosal biopsy are essential to confirm the diagnosis and to exclude IBD-associated colitis. These diseases include microscopic colitis, ischemic colitis, segmental colitis associated with diverticula, radiation colitis, diversion colitis, eosinophilic colitis and Behcet's colitis.

TREATMENT: In many cases the treatment is empirical and often the therapy and outcome depend on the severity of the disease.

Key Words:
 Colitis, Inflammation, Infectious diarrhea, Chemical agents.

Introduction

The term "Colitides" includes a variety of inflammatory diseases of the colon which may be differentiated from inflammatory bowel disease (IBD) by their clinical, endoscopic and histological characteristics[1,2]. A wide range of etiologies and pathogenic mechanisms underlie colitides: infectious, non-infectious and idiopathic etiologies (Table I).

Clinical presentations include chronic watery diarrhea, abdominal pain and intermittent rectal bleeding. Constitutional symptoms are typically absent and laboratory data are often non-specifically altered. Endoscopic evaluation and mucosal biopsy are essential to confirm the diagnoses and to exclude IBD-associated colitis. In many cases the treatment is empirical and there is a need for future research using randomized controlled trials.

Microscopic Colitis

Microscopic colitis (MC) is an inflammatory condition of the colon causing chronic diarrhea, cramping and bloating. It has now emerged as a common cause of chronic diarrhea, especially in elderly woman, characterized by macroscopically normal colonic mucosa with histopathological features of aspecific inflammation. MC comprises two entities: collagenous colitis (CC) and lymphocytic colitis (LC). They are similar in clinical presentation but differ histologically.

The MC is found worldwide. The frequency of MC has been estimated to be 4.2-10.0 per 100,000[3,4] with a peak in 60-70 year-old individuals with a noticeable female predominance for CC[5]. Rarely MC can present in childhood.

The mechanism involved in the development of MC is unknown. There seems to be an association with bile acid malabsorption, infectious agents, nonsteroideal anti-inflammatory drugs (NSAIDs), other drugs like acarbose, aspirin, Cyclo3 fort, lansoprazole, ranitidine, sertraline and ticlopidine assumption, smoking, and autoimmune or auto-inflammatory conditions, like thyroid disorders, celiac disease, diabetes mellitus and rheumatoid arthritis[6-8].

The clinical presentation is characterized by chronic or recurrent, non bloody, watery diarrhea, often associated with nocturnal diarrhea, diffuse abdominal pain, and weight loss[6,7]. Fatigue, nausea and fecal incontinence are other associated symptoms. The onset of disease can be sudden and mimic infectious diarrhea. The clinical course is variable, benign with chronic relapsing.

Endoscopically taken biopsy is required for the diagnosis. The biopsies must be random taken. On histology, both CC and LC, show lymphocytic infiltration of the lamina propria and epithelium. Collagenous colitis is differentiated from LC by the presence of marked thickening of the subepithelial collagen layer[9], together with a chronic mononuclear inflammation in the lamina propria, and epithelial cell damage, with an occasionally increased number of intraepithelial lymphocytes.

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Table I. Classification.

Classification
Microscopic colitis
Ischemic colitis
Diversion colitis
***Clostridium* difficile infection**
Infectious colitis: • Campilobacter jejuni
• Salmonella sp
• Shigella
• Escherichia coli
• Yersinia
• Chlamydia trachomatis
• Neisseria
• Tuberculosis
CMV
Unusual type of cobitide: • Radiation proctitis
• Chemical/medical induced colitis (NSAIDs, disinfectants, antineoplastic agents, eosinophilic colitis)

The thickened subepithelial collagen layer in CC is >10 μ, in contrast with a normal basal membrane of <3 μ. The thickening of the collagen layer may be variable and is most prominent in the ascending or trasverse colon or rectum[10]. The diagnostic feature of LC are an increased number of intraepithelial lymphocytes (<20/100 surface epithelial cells), with surface epithelial cell damage, infiltration of lymphocytes and plasma cells into the lamina propria, with normal collagen layer[11]. Laboratory tests are mainly non-diagnostic and only moderately elevated C-reactive protein, erythrocyte sedimentation rate, or mild anemia are found. Fecal calprotectin can be slightly elevated.

The treatment consists in a stepwise approach. The first step is avoid NSAIDs and other possible precipitant agents and rule out coexisting celiac disease with serology. The first line medical-therapy for patients with MC is nonspecific antidiarrheal therapy such as loperamide, with dose ranging from 2 to 16 mg per day. For non-responder patients it is recommended budesonide (9 mg/d the first month followed by 6 mg/d and 3 mgd the second and third months respectively)[5]. After the establishment of the remission the patient can use loperamide or bismuth salicylate even if they failed to respond to these agents in the past. In clinical practice tapering doses of budesonide (3-6 mg/d) have been successfully used as maintenance therapy in order to control symptoms[5]. There is only one study assessing the use bismuth subsalicylate in patients with MC that recommends it as second-line therapy and generally in patients with milder disease[8]. The use of bile-acid binder agents is reasonable in those with known bile-acid malabsorption and those in whom MC developed after cholecystectomy[8]. The use of 5-amino-salicylic-acid (5-ASA) is recommended only when the treatment with more potent agents such as budesonide has not been successful. Antibiotics such as metronidazole or erythromycin have been used but not in a controlled fashion. Probiotic treatment shows uncertain results and need further evaluations[12]. Rarely when all medical options have been unsuccessfully exhausted, MC can be treated surgically.

Ischemic Colitis

Ischemic colitis (more appropriately called "vascular disease of the colon") is the most common type of intestinal ischemia, consequence of acute or chronic blockage of blood flow though arteries that supply the large intestine. It is most common in the elderly and its prevalence increase with age. Its etiopathogenesis includes vascular factors such as ischemia and embolus, intestinal factors such as constipation, irritable bowel syndrome and intestinal surgery as well drugs' administration such as antibiotics, appetite suppressants (phentermine), chemotherapeutic agents, medications for constipation, decongestants (pseudoephedrine), cardiac glucosides, diuretic, ergot alkaloids, hormonal therapies, statins, illicit drugs, immunosuppressive drugs, laxatives, NSAIDs, psychotropic medications, serotonin agonist/antagonist and vasopressors.

Two mechanisms may cause bowel ischemia: the first and most common is diminished bowel perfusion due to low cardiac output (heart diseases or cases of prolonged shock); the second is the occlusive disease of the vascular supply to the bowel due to atheroma, thrombosis, or embolism in which collateral circulation is not adequate. The morphologic pattern accounts for 3 groups: (1) transmural infarction, (2) mural infarction (extending from the mucosa into the muscularis) (3) mucosal infarction (ischemic damage confined to the mucosa).

The incidence is underestimated because many mild cases may remain unreported. The prognosis is more favorable that than of the other forms of mesenteric ischemia. No racial or ethnic association has been reported. The male-female ratio in ischemic colitis is approximately 1:1[13].

Ischemia has a wide range of features ranging from transient intramural and submucosal hemorrhage and edema to gangrene. So far ischemic col-

itis may present as two major clinical patterns: gangrenous and non-gangrenous. In the nongangrenous form lesions may be transient and reversible, or progress to chronic and irreversible strictures or chronic segmental colitis. Mild to moderate abdominal pain is present in about 60% of cases, usually described as cramps. Patients have often an urgent defecation. The pain may be associated with diarrhea, frequently followed by bleeding. The blood may be red or maroon and mixed with stool. Peritoneal signs onset only later in the course of the disease. The white cell count is generally raised but significant ischemic injury can be present without leukocytosis. If acute ischemia leads to infarction, fever, neutrophilia and metabolic acidosis may be present.

The diagnosis depends on evaluation of the patient and an accurate biochemical, radiological and endoscopic assessment. The radiologic findings are aspecific. Plain radiographic imaging often reveals dilatation of the colonic tract in the early stage disease. Barium enema examination during the acute stage of a vascular insult demonstrates spasm associated with thickening and blunting of the mucosal folds. In the healing phase when fibrosis sets in associated flattening and rigidity of the intestinal wall may be observed. Barium enema should be avoided where there is the suspicion of gangrene or perforation. CT even though cost-effective stays the best diagnostic option for the differential diagnosis of other of abdominal pain causes. Ultrasonography is a noninvasive technique that may provide useful information in particular for chronic mesenteric ischemia. Color flow Doppler sonography is effective in demonstrating flow disturbances associated with tortuosity and stenosis at the origin of the celiac axis. Angiography has a limited role. Colonoscopy, although invasive is the most sensitive diagnostic test for ischemic colitis.

If the physical examination does not suggest gangrene or perforation, the patient is treated expectantly: mild cases can be managed with liquid diet, close observation and antibiotics on demand. For inpatients a combination of intravenous fluids and bowel rest is recommended to reduce intestinal oxygen requirements. Parenteral nutrition should be considered for patients who do not respond immediately. Digitalis and other vasopressors should be withdrawn or minimized if possible. About 20% patients require surgery (sepsis, signs of peritoneal irritation, diarrhea and bleeding lasting more than 10-14 day, endoscopic evidence of full-thickeness ischemia, or protein-loosing enteropathy).

Diversion Colitis

Endoscopic evidence of diffuse colitis can be found in 70% to 91% of patients with fecal diversion[14,15]. Findings may be mild to severe and include mucous plugs, friability, petechia, erythema, ulcers, exudate, and nodules or polyps[16]. A significantly smaller percentage of patients experience symptoms such as rectal pain or discomfort, bleeding, and discharge. Lymphoid follicular hyperplasia can be found on double-contrast barium enema study in 30% of diverted patients. This often resolves after re-anastomosis[17]. Histology do not-dependent on the length of diversion but related to the condition of the colonic mucosa prior to it[18]. Endoscopic biopsies of previous normal colon may reveal diffuse mild acute and chronic inflammation with or without mild crypt architectural abnormalities, crypt abscesses, atrophy, or follicular lymphoid hyperplasia[19,20]. Lymphoid follicular hyperplasia is described as a distinctive pathologic finding in patients with diversion colitis despite the previous condition of the colon. 90 Enlarged germinal centers of B-cell and T-cell lymphocytes are found consistently in pediatric patients but not in all adults with diversion colitis[21]. Diversion colitis is thought to be due to absence of a nutritional factor provided by the fecal stream or to an alteration in bacterial flora: by disrupting the fecal stream distal colonocytes are deprived of their primary substrate, resulting in inflammation or possibly a change in bacterial populations. Several reports of successful treatment of diversion colitis using short-chain fatty acids (SFCA) enemas seem to support this hypothesis. Moreover restoring the fecal stream cures diversion proctitis. When this is not possible treatment with SCFAs may improve symptoms. The use of 5-ASA enemas and higher concentrations (100 mM) of butyrate may be particularly helpful in diverted ulcerative colitis patients[21].

Clostridium Difficile Infection

Clostridium difficile is an anaerobic, Gram positive and spore-forming organism firstly described in 1930, termed *Bacillus difficilis* for the difficulties in *in vitro* cultures. Initially described as a member of the commensal microbiota in newborns *Clostridium difficile* was identified as the casual agent of antibiotic-associated diarrhea in the 1970[22,23]. Thus it was clear that antibiotic treatment (especially cephalosporins) is the main risk factor for the development of this infection together with advanced age and hospitalization. The clinical presentation of *Clostridium difficile*-asso-

ciated disease (CDAD) can range from an asymptomatic carrier state, colitis with or without pseudo-membranes (with or without bloody diarrhea), and, in its most feared incarnation, fulminant colitis with megacolon or perforation[24,25]. Symptoms occur with the production of two exotoxins, toxin A and toxin B (about 1000 times more pathogenic than toxin A) disrupting the integrity of the colonic mucosa[26]. The incidence and severity of *Clostridium difficile* infection (CDI) are quickly growing in North America and Europe[27] with the evidence of increasing resistance to standard therapy and propensity to relapse. In the light of these evidences there has been a renewed interest in the laboratory diagnosis of this infection, since rapid and accurate diagnosis of CDI is essential for the management of patient and epidemiological monitoring. Initial strategies to detect *Clostridium difficile* consists in anaerobic stool culture, usually with cycloserine cefoxitin fructose agar (CCFA) or similar media with or without a pretreatment alcohol shock step[28]. Although quite sensitive and specific this modality takes up to five days to confirm a negative culture and does not discriminate between toxigenic and non-toxigenic isolates unless further testing strategies. For this reason have been developed different, more sophisticated methods to detect this virulent organism. Historically the cell culture cytotoxicity neutralization assay (CCCN), which detects cytotoxin production in monolayers of cells, such as human diploid fibroblasts, has been the gold standard for *C. difficile* detection in the laboratory. However cell culture is labor-intensive and many laboratories have adopted other testing such as enzyme immunoassays (EIAs) for toxins A and B, easier and faster to perform[29-31]. Recent reports have highlighted the lack of sensitivity of the toxin A/B EIAs showing sensitivities as low as 48%[32,33]. Although toxigenic culture of the organism has now been reaccepted as the true gold standard[34], this method requires substantial laboratory resources, and results are not available in a short enough time frame to be clinically useful[33,35,36]. Thus, other approaches improving both the sensitivity and the cost-effectiveness of *C. difficile* testing have been introduced[29,32]. Testing algorithms using a glutamate dehydrogenase (GDH) assay (which has presumptively higher sensitivity but lacks specificity) to screen for *C. difficile* in stool samples with reflex testing using a more specific assay, such as a toxin A/B EIA or the CCCN, have been proposed[37-39]. GDH assays detect antigen present in both toxigenic and nontoxigenic strains of *C. diffi-*

cile directly in stool samples. The time necessary to perform the GDH assay with EIA or CCCN confirmation can be as long as 3 days[40]. Gilligan[41] noted that EIAs often lacks sufficient sensitivity for confirmation of positive GDH assay results. PCR assays for various targets have been developed as a potential replacement for the less-sensitive (EIA) and less-specific (GDH) assays for *C. difficile* detection[42-45]. Such assays include both "home brew" PCR assays and FDA-cleared commercial assays[33,46-48]. Cepheid (Sunnyvale, CA, USA) has recently developed a GeneXpert cartridge-based assay for detection of the *C. difficile* toxin B gene (*tcdB*) directly from stool, which seems to be a promising method to detect quickly the microorganism.

Up to date a prompt diagnosis of CDI is of pivotal importance to establish a valid treatment. Standard pharmacologic treatment for CDI is aimed to achieve adequate bactericidal fecal concentrations. For this purpose oral vancomycin and metronidazole are considered the agents of choice. Metronidazole has been shown to have a 98% cure rate and is comparable to vancomycin in terms of efficacy[49,50]. According to the most recent treatment guidelines from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America, the recommended pharmaco-therapeutic option is stratified based on disease severity. For mild-to-moderate cases of *C. difficile* infection metronidazole 500 mg 3 t.i.d. per os for 10-14 days is the preferred regimen[51]. In severe cases of *C. difficile* infection oral vancomycin 125 mg q.i.d. for 10-14 days is recommended. In complicated cases oral vancomycin 500 mg q.i.d. with or without intravenous metronidazole 500 mg administration every 8 hours is recommended. A major complication of CDI management is the relapse which occurs in approximately 20% of all patients treated with metronidazole or vancomycin. Relapse is characterized by recurrence of symptoms identified by the patient as nearly identical to the previous although they can be either more or less severe. The recent guidelines recommend management of a first CDI relapse analogous to the original bout (oral vancomycin or metronidazole) though relapse infections should be treated with oral vancomycin because long-term use of metronidazole may cause peripheral neuropathy[52]. Alternative or ancillary agents for relapses include rifaximin (as a "chaser" after pulse vancomycin)[53], nitazoxanide[54], and intravenous immunoglobulins[55]. The most promising experimental agents that are for

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reducing relapses are fidaxomicin (two phase III trials completed with good results)[56], and monoclonal antibodies to toxin A and B given intravenously with a standard regimen of vancomycin or metronidazole[57].

Probiotics given for *C. difficile* include *Saccharomyces boulardii* and multiple *Lactobacillus* preparations. These are not recommended since are generally harmless, although several cases of *S. boulardii* fungemia have been reported primarily in immunocompromised hosts[58]. *Lactobacillus rhamnosus* bacteremia has also been reported in consumers of *Lactobacillus* GG, but this is also rare[58]. Moreover it has to be noted that oral vancomycin is active versus all *Lactobacilli*.

A treatment for relapse CDI that nearly always works is fecal biotherapy-transplant of stool from healthy donor to the patient with multiple relapses and refractory to all forms of therapy[59-62]. The donor specimen is delivered by nasogastric tube or by colonoscope or enema. Results from 100 reported cases showed a definitive cure in 89% of those; before treatment most patients had recurrent diarrhea for over six months and yet the first post-transplant stool resulted to be normal[60].

Infectious Colitis

Infectious colitis are very common in general practice and represent a public health issue in both developed and non-developed countries. Elderly persons, children and immune-compromised subjects are susceptible to this kind of infections. Transmission modes encompass the fecal-oral route, animal hosts, ingestion of contaminated food and water, and close human-to-human contact. Direct contact infection is more common in crowded areas where compromised hygiene is (i.e., day care centers and nursing homes)[63]. Infectious colitis are divided into non-inflammatory and inflammatory. Non-inflammatory colitis are caused by pathogens (i.e., *enterotoxigenic Escherichia coli* and *Staphylococcus*) that alter normal absorptive and secretory functions of the bowel leading to watery diarrhea without fever. Inflammatory colitis are characterized by bloody and mucous-purulent diarrhea often associated with fever, tenesmus, and severe abdominal pain. Common pathogenic bacteria causing inflammatory diarrhea include *Campylobacter*, *Salmonella*, *Shigella*, *enteroinvasive* and *enterohemorrhagic Escherichia coli*, *Yersinia*, *Chlamydia*, *Neisseria*, and *Mycobacterium Tuberculosis*. In this paragraph we focus on the most common pathogens.

Campylobacter (C.) jejuni is a curved, highly motile micro-aerophilic Gram-positive rod, one of the major causative agent of infectious diarrhea to date[64]. Transmission occurs most frequently through contaminated poultry and acquired by eating under-cooked chicken. The reservoir for this organism is huge, since different kinds of animals can be infected and includes cattle, sheep, swine, birds, and dogs. Clinical illness manifests as frank dysentery with few patients exhibiting watery diarrhea or asymptomatic excretion[64]. The most common clinical symptoms are diarrhea and fever (90%), abdominal pain (70%), and bloody stool (50%). The clinic feature last less than 1 week although symptoms can persist for 2 weeks or more and relapses occur in as many as 25% of patients[65]. Complications of *Campylobacter* infections are rare and include gastrointestinal hemorrhage, toxic megacolon, pancreatitis, cholecystitis, hemolytic-uremic syndrome (HUS), meningitis, and purulent arthritis. Reiter and Guillain-Barré syndromes are conditions that may follow *C. jejuni enterocolitis*.

Most patients with mild to moderate *C. jejuni enterocolitis* do not need antibiotic therapy because the infection is usually self-limiting. Treatment (quinolonic antibiotics) is reserved to patients with dysentery and high fever suggestive of bacteremia and debilitated or immune-compromised subjects.

Salmonella species are gram-negative, rod-shaped bacilli, members of the Enterobacteriaceae family. *Salmonella typhi* and *Salmonella paratyphi* cause typhoid fever, and other *Salmonella species* are associated with gastroenteritis, enterocolitis, and focal infections, such as meningitis, septic arthritis, cholangitis, and pneumonia. *Salmonella* is considered primarily a food-born infection. The major mode of transmission is by the "5 Fs": flies, food (poultry has the highest incidence of *Salmonella* contamination), fingers, feces, and fomites. In Western Countries the two most common serotypes are *Salmonella enteritidis* and *Salmonella typhimurium*. In these regions the prevalence of the infection is estimated as 20 cases per 100,000 population. Clinical symptoms of *S. typhi* infection (typhoid fever), include sustained hectic fever, delirium, abdominal pain, splenomegaly, persistent bacteremia, and "rose spot" skin rashes[64]. Typhoidal disease is not truly an intestinal disease and has more systemic than intestinal symptoms. The liver, spleen, and lymph nodes (including Peyer's patches) become involved and may result in focal areas of liver and spleen necro-

sis, acute cholecystitis, and micro-perforations in the terminal ileum. Erosion into blood vessels may produce severe intestinal hemorrhage. A 10- to 14-day course of a quinolonics is highly effective for its treatment and these antibiotics have become the treatment of choice in eradicating the carrier state also. Non-typhoidal *Salmonella* infections arise with nausea, vomiting, abdominal cramps, and diarrhea. Diarrhea can vary from loose stools to dysentery with grossly bloody and purulent feces. Symptoms arise 8 to 48 hours after ingestion of contaminated food. The illness lasts for 3-5 days in patients with gastroenteritis and 2-3 weeks in those with enterocolitis. Most cases of these enterocolitis are self-limiting and do not require antibiotic therapy as well. Exceptions include patients with lymphoproliferative disorders, malignancy, AIDS, transplantation, prosthetic implants, valvular heart disease, hemolytic anemia, extreme ages of life, and symptoms of severe sepsis.

Shigellae are a group of Gram-negative enteric micro-organisms included in the Enterobacteriaceae family causing a broad spectrum of gastrointestinal illness ranging from mild diarrhea to life-threatening dysentery. There are four major subgroups: *Shigella (S.) dysenteriae* (group A), *S. flexneri* (group B), *S. boydii* (group C), and *S. sonnei* (group D)[63]. Shigellosis is a worldwide endemic disease and is responsible for more than 650,000 deaths each year[66]. In Western Countries *S. sonnei* is the most common serotype and causes nearly 80% of bacillary dysentery. *S. dysenteriae* and *S. flexneri* are the species causing endemics and pandemics in developing countries. *Shigella* is highly contagious and requires only a small number of ingested inocula to yield clinical symptoms in infected subjects[67]. The disease is spread readily through person-to-person contact with fecal-oral and oral-anal contacts. The classic presentation of bacillary dysentery includes crampy abdominal pain, rectal burning, and fever associated with multiple small-volume bloody mucoid stools. All *Shigella species* are capable of elaborating Shiga toxin an enterotoxic, cytotoxic, and neurotoxic toxin[68]. Initial diarrhea is watery without gross blood and is related to the action of enterotoxin. The second phase is associated with tenesmus and small volume bloody stools that occur 3 to 5 days after onset and corresponds to invasion of the colonic epithelium and acute colitis. Unfortunately severe complications are relatively common and include intestinal perforation, megacolon, septic shock, HUS (hemolytic-uremic syndrome), profound dehy-

dration, hypoglycemia, hyponatremia, seizures, and encephalopathy[69]. Treatment is initiated with volume resuscitation and specific therapy for complicating conditions such as seizures, encephalopathy, and intestinal perforation. Antibiotic treatment is always indicated for Shigella infections because of its ease of transmission and propensity to cause life-threatening illness[66].

Apart from the afore-mentioned illnesses a particular kind of infections is represented by sexually transmitted proctitis. They are still a significant public health problem both worldwide and especially in Europe[70]. although due to health promotion campaigns in the 1980`s their incidence has been significantly reduced[71]. Common causes of proctitis include infection with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, herpes simplex virus (HSV), and *Treponema pallidum*. Symptoms depend on the specific infective agent and/or pathological underlying process and indistinguishable from those of inflammatory bowel diseases. The most common symptom of proctitis is a frequent or continuous urgent defecation. Other symptoms include anal-rectal pain or discomfort, anal discharge, which may be purulent, mucoid or blood-stained, tenesmus, rectal bleeding and constipation. Proctocolitis present with the symptoms of proctitis and diarrhoea, abdominal pain, and bloating. Systemic symptoms such as fever may also occur. Different pathogens typically infect different sites: HSV and syphilis infect the stratified squamous epithelium and are commonly seen in the peri-anal area and at the anal verge.

Infections occurring between the anal verge and the ano-rectal (dentate) line tend to be extremely painful owing to abundance of sensory nerve endings in this area. *Chlamydia* and *Neisseria gonorrhoeae* infect columnar epithelium in the rectum that has few sensory nerve endings thus infections sparing the anus may be painless. It is a common practice that patients with acute proctitis and history of anal intercourse to be treated empirically for Chlamydia and gonorrhea while awaiting microbiological tests useful to start the appropriate therapy.

Cytomegalovirus in Immunosuppressed Patients

Cytomegalovirus (CMV) is an ubiquitous herpes virus that infects 60%-100% of humans[72]. Primary CMV infection in immune competent individuals presents most commonly as asymptomatic or a benign febrile infectious mononucleosis-like syndrome. When CMV infection occurs

in immunocompromised individuals such as transplant recipients, oncologic or HIV patients, the disease may have with high morbidity may and, in some cases, may be life-threatening[72]. The classic clinic of CMV infection in those patients includes fever, bone marrow suppression, and organ invasive diseases (Table II)[72]. These have been traditionally categorized either as CMV syndrome (fever with bone marrow suppression) and tissue invasive CMV disease (which may involve virtually any organ[73]. The most common organ system involved during CMV disease is the gastrointestinal tract (in the form of CMV gastritis, esophagitis, enteritis, and colitis), accounting for over 70% of tissue invasive CMV disease cases in immune-suppressed people. Patients more commonly have diarrhea but can present abdominal pain, fever and weight loss also[74]. Life-threatening complications may also occur including massive lower gastrointestinal bleeding, colonic perforation, acute appendicitis, ileo-cecal obstruction and toxic megacolon. Cytomegalovirus colitis (CMVC) has a considerable morbidity and mortality with a very poor prognosis since it is approximately estimated that the median survival time is 18-71 weeks. Endoscopic patterns of CMVC in immune-compromised patients are heterogeneous although sub-epithelial hemorrhage, colitis and/or ulcers can be typical. Its appearance could also mimic ulcerative colitis, Crohn's disease and pseudomembranous colitis. Given these evidences it is clear that CMV infection prevention with antiviral prophylaxis is crucial in those cohort of patients. Currently valganciclovir prophylaxis is the most common approach and this drug is also used as first-line therapy for those patients with severe CMV disease. The duration of treatment should be individualized depending on clinical and laboratory parameters such as the decline of CMV load in the blood as measured by rapid and sensitive molecular testing.

Unusual Types of Colitides

With the term "unusual" we refer to particular types of colitides which include: (1) radiation proctitis; (2) chemical induced/medication induced colitis and (3) eosinophilic colitis.

Radiation Proctitis

Arises from pelvic radiotherapy for several gynecologic, urologic, and rectal cancers. It has been estimated that 75% of subjects receiving pelvic radiotherapy, experience rectal symptoms during treatment and almost 20% evolve to chronic proctitis[75]. In addition 5% may develop perirectal fistulas, strictures, or incontinence. The symptoms are usually related to loose stools, urgency, bleeding, pain, or tenesmus. Although these acute symptoms have been shown to progress throughout treatment endoscopic and histologic findings appear to peak after 2 weeks of radiotherapy and may stabilize or regress through completion of treatment[76]. Endoscopy in this setting can reveal friability and granularity, pallor, erythema, or prominent submucosal telangiectasias[77]. These histologic findings in the acute phase typically show epithelial meganucleosis, fibroblastic proliferation, and absence of mitotic activity, different from the chronic findings of severe vascular changes such as telangiectasia of capillaries, platelet thrombus formation, and narrowing of arterioles always accompanied by lamina propria fibrosis and crypt distortion[78].

Numerous therapeutic agents have been evaluated in order to treat this condition and actually two approaches can be taken. First is the prevention: the

Table II. Direct and indirect clinical effects of CMV in immunosuppressed patients.

Direct effects	Indirect effects

1) CMV syndrome:
    Fever
    Myelosuppression
    Malaise
2) Tissue-invasive CMV disease:
    Gastrointestinal disease (colitis,
    esophagitis, gastritis, enteritis)
    Hepatitis
    Pneumonitis
3) CNS disease
4) Retinitis
	1) Acute allograft rejection (in transplanted patients)
	
	2) Chronic allograft rejection (in transplnted patients)
	
	3) Vanishing bile duct syndrome
	
	4) Opportunistic and other infections
	    Fungal superinfection
	    Nocardiosis
	    Bacterial superinfection
	    Epstein-Barr virus and PTLD
	    HHV-6 and HHV-7 infections
	5) Vascular thrombosis

drug is administered before and during the radiation treatment and aimed at averting the onset of symptoms. The second more common approach consists in the pharmacotherapy after the symptoms onset; this may apply to both the acute and chronic phase. These two approaches use the same drugs and include anti-inflammatories such as various 5-aminosalicylic acid (5-ASA) preparations and steroid preparations; sucralfate which seems to be build a protective barrier against the radiant insult and promote epithelial healing; short-chain fatty acid (SCFA) enema preparations since they act as the main energetic source for colorectal mucosa, thus, it was hypothesized that their addition might be useful in overcoming some of the toxic effects of radiation therapy; antioxidant vitamins such as vitamin E and vitamin C. Surgical therapy remains an option for refractory cases and may be required in the setting of complications like obstruction, perforation, or fistula formation.

Chemical/Medical Induced

Colitis is a peculiar kind of bowel inflammation caused by drugs and medications. Among the latter some deserve a particular mention:

- *NSAIDs* which may cause affect both the colon and rectum. In fact they may activate the inflammatory bowel disease pathogenic process, and be the primary cause of collagenous and lymphocytic colitis; they can also precipitate until the severe complications of diverticular disease[79-81]. nonspecific colitis associated with ulcerations may also be seen, and this may be ischemic[82]. Patients may present with bloody diarrhea, weight loss, iron deficiency anemia, or abdominal pain. Symptoms often resolve soon after the drug is discontinued[83]. Strictures of the colon may also result from NSAIDs use. These strictures tend to be short and have diaphragm-like strictures in the right colon. They are often multiple and associated with sustained-release NSAIDs. Although they may cause obstruction and require surgical resection successful treatment with balloon dilatation has been reported[84];
- *Disinfectants* which can cause acute toxic injury of the distal colon and rectum. Other rectally administrated agents such as endoscopy cleaning solutions, radiologic contrast material, hydrogen peroxide, soaps, formalin, hydrofluoric acid, alcohol, ammonia, lye, hot water, and herbal substances, can cause chemically-induced colitis. Patients present with abdominal pain, hema-

tochezia, and fever. History of a recent procedure or self-administered enema is critical for the presumptive diagnosis as long the endoscopic findings are variable and non-specific;
- *Antineoplastic Agents and Cyclosporine* are the most common cause of chemical/medical induced colitis. Patients may present with abdominal pain, severe watery diarrhea, or hematochezia. 5-Fluorouracil may cause inflammation and ulceration of the upper gastrointestinal tract as well as the colon[85]. Therapy includes bowel rest, intravenous hydration, and broad-spectrum antibiotics in order to prevent superimposed infections[86,87].

Eosinophilic Colitis (EC)

Is a rare manifestation of the eosinophilic gastrointestinal disease spectrum. Primary eosinophilic gastrointestinal disease (EGID) resembles a rare spectrum of gastrointestinal disorders characterized by an inflammatory panel rich in eosinophils, without evidence of known causes for eosinophilia such as parasitic infection, drug reaction, or malignancy[88]. The disease can affect any segment or combination of segments of the gastrointestinal tract. Since secondary eosinophilic inflammation may occur in numerous gastrointestinal disorders such as IgE-mediated food allergy, gastroesophageal reflux disease, and inflammatory bowel disease, the true incidence and prevalence of primary EGID remains largely unknown. EC represents the least frequent manifestation of EGID whether or not it presents with disease in other segments of the gastrointestinal tract[89]. EC appears to have a bimodal distribution that affects newborns with a relatively high prevalence and a separate group of young adults with no gender preference[88]. EGID has three hallmarks including: peripheral eosinophilia (typically present in the range of 5-35%), segmental eosinophilic infiltration of the interested gastrointestinal tract, and functional abnormalities[90]. EC results in diarrhea and the transmural form has been associated with volvulus, intussusception, and even perforation; the involvement of the intestinal serosa may elicit as ascites. No consensus exists for EC diagnosis although most Authors have used a diagnostic threshold of 20 eosinophils per high-power field for the histologic analysis. Interestingly normal values of tissue eosinophils vary widely between different segments of the colon, ranging from < 10 eosinophils per high-power field in the rectum to > 30 in the cecum[91] thus the site of the biopsy is of critical importance for the diagnosis. Prominent tissue eosinophilia in the colon may result from a number

of conditions and EC remains therefore a diagnosis of exclusion. Drug-induced EC has been described in response to clozapine, carbamazepine, rifampicin, NSAIDs, tacrolimus, and gold. EC has also been associated with autoimmune connective tissue disease including scleroderma, dermatomyositis and polymyositis[92,93] as well as with allogenic bone marrow transplantation and the rare Tolosa-Hunt syndrome that features inflammatory ophthalmoparesis. The idiopathic hypereosinophilic syndrome (HES) may also affect the colon but this rare condition presents with sustained and marked peripheral eosinophilia with end-organ damage that extends beyond the gastrointestinal tract (e.g. heart and skin). The etiology of primary EC remains largely unknown.

Corticosteroid therapy has formed the backbone for initial management and it has proven to be the most effective instrument for symptom control[88]. Up to 90% of cases will respond within 2 week to the treatment however relapse is frequent and requires repeated courses of this treatment and often leads to steroid dependence.

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