ORDER IN CHAOS: A CONDENSED REVIEW OF THE LITERATURE ON INFLAMMATORY BOWEL DISEASE

R Mejdi[1], H Osakwe[2]
[1]Department of Pediatric Surgery – University of Medicine and Pharmacy Timisoara
[2]Department of Pediatric Surgery – County Emergency Hospital Arad

Abstract

This article intends to be a condensed and simplified review of the literature on inflammatory bowel disease. The chaos of prolific and nonetheless controversial genetic, immunologic and epidemiologic studies has been conscientiously evited in favor of issues of direct interest to the pediatric surgeon.

Keywords: inflammatory bowel disease, Crohn disease, ulcerative colitis, terminal ileitis, backwash ileitis, colorectal carcinoma, extraintestinal manifestations, ASA, pouchitis, endoscopic surveillance.

Introduction

Inflammatory bowel disease (IBD) is a set of chronic non-specific inflammatory disorders of the GI tract comprising primarily Crohn disease (CD) and Ulcerative colitis (UC); and additionally microscopic ulcerative colitis, microscopic lymphocytic and collagenous colitides. The intuitive clinical impression of CD and UC being variations on the same theme rather than distinct entities is corroborated by the overlap of their pathogenesis, clinical presentations, radiological and histopatho-logical findings. Moreover, in 10-20% of colitides a definitive diagnosis cannot be established, hence the label of "indeterminate IBD".

Alternative denominations- present and obsolete.

Crohn disease	Ulcerative colitis
Regional enteritis	Colitis ulcerosa
Terminal ileitis	Proctocolitis
Granulomatous ileocolitis	Ulcero-hemorrhagic rectocolitis
Chronic granulomatous enterocolitis	Bloody flux

Epidemiology

There is a marked discrepancy in the distribution of IBD with north-to-south and urban-to-rural gradients. IBD being most prevalent in Caucasians from northern industrialized countries including the US, UK and Scandinavia; and less prevalent in South America, Asia and Africa.

Interestingly, IBD is 2-4 times more common in Ashkenazi Jews.

Recently, several studies tend to mitigate such clear-cut epidemiological data and demonstrate the closing of the racial, ethnic and socio-economic gap, probably due to "westernization" of lifestyle.

IBD – Incidence, prevalence and M: F ratio.

IBD	INCIDENCE	PREVALENCE	M:F ratio
CROHN DISEASE	5 : 100.000	50 : 100.000	1 : 1.2
ULCERATIVE COLITIS	15 : 100.000	150 : 100.000	1.2 : 1

IBD has a bimodal age distribution with a first peak [15-30 y.o.] and a later smaller peak [60-80 y.o.]. 10% of patients are younger than18 years.

IBD in the pediatric population must be regarded differently from the disease in adults for four major reasons: (1) IBD is relatively more severe in children, (2) Failure to thrive in infants and young children, and delayed growth during prepuberty are issues to be addressed, (3) Chronic disease and a toilet-centered life accentuate the usual emotional problems of the adolescent, and last but not least

(4) The malignisation potential of the colonic lesions is amplified after long-standing colitis in childhood.

Etiopathogenesis

A positive family history is considered to be the most important risk factor for developing IBD. The risk of CD in first-degree relatives of a CD patient is 10-14 times higher than in the general population, with the risk of UC being 8 times higher. In CD, but not UC, affected patients are more likely to be siblings than first-degree relatives.

Based on studies of monozygotic twins, the coefficient of hereditability of CD is high (equivalent to that in type 1 diabetes mellitus). In UC, it is much lower, which argues for a stronger environmental component in susceptibility.

Oral contraceptives and isotretinoin (Accutane) have been identified as risk factors for CD and UC respectively. Patients with CD are more likely to be smokers, whereas smoking and appendectomies have a negative association with UC.

The etiopahogenic contribution of ethnicity, dietary, microbial, immunologic, environmental, vascular, and even psychosocial factors is still a subject of speculative debate and controversy.

Macroscopic and microscopic pathology

Crohn Disease is a chronic inflammatory condition that may potentially affect any segment of the GI tract from the mouth to the anus, but has a particular tendency to affect the terminal ileum and ascending colon (ileocolonic disease). The small intestine is involved in 90% of patients younger than 20 years old, whereas colonic involvement is more common in patients older than 40 years old. A useful mnemonic aphorism to remember is that *the caliber of the intestine involved grows with the patient*

Microscopically, the initial lesion starts as a focal inflammatory infiltrate around the crypts followed by ulceration of the superficial mucosa. Later, the inflammatory process involves deep layers and begins to organize into non-caseating granulomas. These granulomas are transmural and extend into the mesentery and the regional lymph nodes. Although granuloma formation is pathognomonic of Crohn disease, absence does not exclude the diagnosis.

Macroscopically, the involved mucosa suffers hyperemia and edema. Later, discrete superficial ulcers form, which become deep serpiginous ulcers located transversally and longitudinally over an inflamed mucosa, giving it the appearance of a cobblestone. Aphtous ulcers are characteristic for CD and are most frequently sited in the mesenteric border of the terminal ileum. The lesions in CD are often segmental, being separated by normal intervening mucosa, and are often referred to as skip lesions.

Ulcerative Colitis can manifest as proctitis in 25% of cases (lesion confined to the rectum), as proctosigmoiditis (involvement of rectum and sigmoid colon), as left-sided colitis (lesion distal to splenic flexure) and as pancolitis, which occurs in 10% of patients (lesion extends proximal to splenic flexure or involves the entire colonic frame). The small intestine is never involved, except when the distal terminal ileum is subjected to a superficial non-ulcerating inflammation; in the presence of a severely incompetent ileocecal valve, a condition referred to as backwash ileitis and arising in 10% of patients with pancolitis.

Ulcerative colitis is characterized by a uniform neutrophilic infiltrate along with crypt abscesses and crypt distortion (cryptitis). These lesions are confined to the mucosa, with no intervening normal segments. Granulomas do not occur in ulcerative colitis.

Even with less than total colonic involvement, the disease is strikingly and uniformly continuous. As the disease becomes chronic, the colon becomes a rigid foreshortened tube that lacks its usual haustral markings, leading to the lead pipe appearance observed on barium enema.

Crohn disease vs. Ulcerative colitis – comparative pathology.

	Crohn disease	**Ulcerative colitis**
Rectal involvement	+++	++++
"Skip lesions"	+++	-
Transmural involvement	+++	+
Granulomas	+++	++
Goblet cells	+++	-
Crypt abscesses	++	+++
Perianal disease	+++	-
"Cobblestone" mucosa	+++	+

Clinical presentation

Crohn disease presents with diarrhea, abdominal pain and tenderness in the RLQ, fever, weight loss and asthenia.

Intestinal obstruction is a frequent complication. Initial ileus is caused by edema and mucosal spasm. It is intermittent and often reversible with conservative measures and anti-inflammatory agents. As the disease progresses, the obstruction becomes chronic and intractable due to fibrosis, luminal narrowing and stricture formation leading to less diarrhea and more constipation.

Fistula formation is also a frequent complication of colonic CD. Fistulae are classified into: benign, nuisance and intractable. Benign fistulae include ileoileal, ileocecal and ileosigmoid fistulae, which might produce only mild or moderate diarrhea or even remain asymptomatic for years. Nuisance fistulae include cologastric (feculent vomiting),

coloduodenal, enterovesical (recurrent UTI, pneumaturia), enterovaginal (feculent vaginal discharge) and enterocutaneous fistulae (feculent soiling of the skin). Such fistulae must be sealed to eliminate their symptomatic nuisance and pathophysiologic consequences, but neither the complications nor the underlying bowel disease is severe enough to require surgery.

A last set of frequent complications of CD is comprised by anal and perianal lesions. These include fissures in ano (multiple and indolent), hemorrhoids, skin tags, perianal abscesses, ischiorectal abscesses, fistula in ano (may be multiple) and anorectal fistulae.

Ulcerative colitis presents with rectal bleeding and diarrhea with frequent discharges of watery stool mixed with blood, pus and mucus associated with tenesmus and rectal urgency, and even anal incontinence. 2/3 of patients experience abdominal cramping and variable degrees of fever, vomiting, weight loss and dehydration. Mild disease may be manifested only by an increase in the frequency or the decrease in the consistency of stools, and few patients complain of paradoxical constipation. The abdomen is tender in the hypogastrium or LLQ.

Several disease activity indices and scoring systems have been designed for the evaluation of the severity and progression of IBD. Truelove and Witt devised a simple classification to assess UC severity based on six criteria. The Crohn's disease Activity Index (CDAI) was developed for the American National Cooperative Crohn's Disease Study and has been subsequently used in the majority of subsequent clinical trials, before it evolved into the Severity-Activity Index (SI) of Goebell et al. Other popular and less popular scoring systems include the Vienna classification for CD and its modified successor; the Montreal classification, IBD Quality of Life Questionnaire (IBDQ) and the Lloyd-Still and Green clinical scoring system for patients with CD and UC.

Vienna and Montreal classification for Crohn disease.

Age at diagnosis	A1 < 40 yrs	A1 < 16 yrs
	A2 > 40 yrs	A2 [17-40 yrs]
		A3 >40 yrs
Location	L1 ileal	L1 ileal
	L2 colonic	L2 colonic
	L3 ileocolonic	L3 ileocolonic
	L4 upper	L4 isolated upper disease [1]
Behaviour	B1 non-stricturing, non-penetrating	B1 non-stricturing, non-penetrating
	B2 stricturing	B2 stricturing
	B3 penetrating	B3 penetrating
		p perianal disease modifier [2]

[1] L4 is a modifier that can be added to L1-L3 when concomitant upper GI disease is present.
[2] "p" is added to B1-B3 when concomitant perianal disease is present.

Ulcerative colitis disease severity based on the Truelove and Witt classification.

CRITERIA	MILD	SEVERE	FULMINANT
Stools (per day)	<4	>6	>10
Hematochezia	Intermittent	Frequent	Continuous
Temperature	Normal	>37.5 C	
Pulse (b/min)	Normal	>90	
Hb	Normal	<75% of normal	Requires transfusion
ESR (mm/h)	<30	>30	

Extraintestinal manifestations of IBD

Extraintestinal manifestations occur in approximately 20% of patients with IBD, and include:

-Episcleritis + uveitis + conjunctivitis

-Skin lesions: there are 2 main skin lesions associated with IBD: Erythema nodosum and Pyoderma gangrenosum. Infectious skin lesions such as herpetic lesions induced by immune suppression are also observed.

Erythema nodosum is a painful, tender, raised, purplish lesion on the anterior surface of the tibia, correlates well with IBD activity and dissipates with treatment.

In contrast, Pyoderma gangrenosum is typically not associated with disease activity, starts as an inflammed patch ranging from 1 to several cms in diameter and then progresses towards ulceration; persisting for months. It shows no amelioration with IBD treatment.

-Urinary complications are most common in Crohn disease, and consist of oxalic nephrolithiasis and fistulous formations involving the ureters and bladder.

-Sclerosing cholangitis is most common in UC. When sclerosing cholangitis has been diagnosed first, perform colonoscopy. If colitis is present, clinical evidence of UC

should be expected within 2 yrs. 5-15% of patients with PSC tend to develop cholangiocarcinoma.

-Gallstones are common in CD and are usually asymptomatic.

-Liver diseases: hepatic steatosis is common, chronic hepatitis and cirrhosis are uncommon

-Venous thrombosis is more common in UC.

-IBD –associated anemia: Fe deficiency anemia due to chronic blood loss + anemia of chronic disease.

-Arthritis**:** the clinician should differentiate medication induced arthropaties from IBD-associated arthritis. IBD-associated arthritis is classified into : (1) axial or central arthritis (5% IBD), consists of ankylosing spondilitis and sacroiliitis, independent of disease activity, often associated with CD, and (2) peripheral arthritis (10% IBD), characterized by non-destructive lesions affecting large joints and seronegative RF, it is further subclassified into: pauciarticular (also known as type 1 arthritis – acute self-limiting attacks < 10 weeks, occur with IBD relapses, associated with other extra-intestinal manifestations), and polyarticular asymmetric (also known as type 2 arthritis – lasts for months-years, independent of IBD activity, usually associated with uveitis.)

Differential diagnosis

Acute appendicitis
Diverticular disease
Gastroenteritis (bacterial, viral, eosinophilic)
Endometriosis
Pelvic inflammatory disease
AIDS (Kaposi sarcoma with chronic diarrhea and colonic involvement)
Antibiotic-associated colitis
Arteriovenous malformations
Colorectal carcinoma
Infectious colitis (proctitis in "gay bowel syndrome")
Intestinal lymphoma (occasionally involves ceaco-ileum)
Intestinal TB
IBS
Ischemic colitis
Pseudomembranous colitis
Radiation-induced colitis
Intestinal motility disorder
Sarcoidosis
Food poisoning
Celiac sprue
C1 esterase deficiency
Giardiasis
Lactose intolerance
Psychiatric disorders (depression, bulimia, anorexia nervosa)
Miscellaneous conditions presenting with diarrhea

Lab studies

-CBC with differential

-Anemia as a consequence of acute or chronic blood loss or malabsorption (Fe, folic acid, vitamin B12) or anemia of chronic disease.

-Leucocytosis, mild in active disease, markedly elevated in the instance of a suppurative inflammation.

-Thrombocytosis.

-ESR and CRP are frequently elevated during active disease.

-Serum Fe, ferritin and total binding capacity are used to assess the iron status of the child.

-Serum folate, B12, Schilling test – terminal ileum function

-Xylose absorption test is sensitive for assessing upper intestinal function.

-72h-fecal fat excretion to document the severity of steatorrhea.

-Hypokalemia reflects the severity of diarrhea.

-Abnormal LFT in sclerosing cholangitis or pericholangitis.

-Protein-losing enteropathy

→ Hypoalbuminemia → Hypocalcemia.

-Stool exam: fecal leucocytes, ova and parasites studies, bacterial pathogens culture.

-Fecal Calprotectin increase is useful to differentiate active disease from other causes of abdominal pain or diarrhea.

-Stool culture to rule out infectious colitis. E. coli H7:O157 (present in hemolytic uremic syndrome). C difficile toxins A+B (present in C. difficile colitis). Salmonella, Shigela, Campylobacter jejuni, Yersinia enterocolitica (50-80% of cases of acute terminal ileitis are due to pseudoappendiceal *Yersinia enterocolitis* infections).

-Positive Blood cultures if peritonitis or fulminant colitis is present.

-Perinuclear antineutrophil cytoplasmic antibodies (pANCA) are positive in UC, and anti-*Saccharomyces cerevisiae* antibodies (ASCA) positive in CD.

Imaging studies

-Plain radiographs of the chest and abdomen are used to demonstrate pneumoperitoneum, pneumatosis coli, toxic megacolon, nephrolithiasis, cholelithiasis, osteopenia, arthritis of the spine or sacroiliitis.

-Barium enema was the first investigative tool to characterize the typical findings in IBD with the use of an extensive descriptive terminology which includes: "stove-pipe" or "lead-pipe" appearance (suggests chronic colitis that has resulted in the loss of colonic haustrae), "rectal sparing" (suggests Crohn colitis in the presence of inflammatory changes in other portions of the colon), "thumbprinting" (indicates mucosal inflammation), and "skip lesions" (suggest areas of inflammation alternating with normal intervening mucosa, again suggesting Crohn colitis). Barium can be refluxed into the terminal ileum in many cases, which can assist in the diagnosis of CD. Barium enema is contraindicated in patients with moderate-to-severe colitis because it risks perforation or precipitation of a toxic megacolon.

- Small bowel series, small bowel follow-through and small bowel enteroclysis are used to assess the severity and length of strictures if present (string sign) and often demonstrate fistulae even in the absence of clinical

evidence. A fistulogram might be obtained by direct insertion of contrast into an enterocutaneous fistula in order to help determine the course of the fistula in anticipation of surgical correction and to assist in guiding the surgical approach.

- CT scan of the abdomen and pelvis has limited use in the diagnosis of IBD. CT is ideal in identifying an intraabdominal abscess, mesenteric inflammation and fistulae, and can be used to guide percutaneous drainage of an abscess.

-Ultrasonography can be an alternative to CT in the evaluation of the intraluminal and extraluminal manifestations of CD.

Imaging procedures include:

- Colonoscopy
- Flexible sigmoidoscopy
- Esophagoduodenoscopy
- Small bowel enteroscopy
- Capsule enteroscopy, is mainly used to locate the source of GI bleeding.

Crohn disease vs. Ulcerative colitis - contrasted findings of conventional radiology and endoscopy.

		Crohn disease	Ulcerative colitis
Conventional Radiology	"Collar button" ulcers	++	+++
	Small intestinal involvement	+++	-
	Discontinuous involvement	+++	-
	Fistulas	+++	-
	Strictures	+++	++
Endoscopy	Aphtous ulcers	+++	-
	Discontinuous involvement	+++	-
	Rectal sparing	+++	-
	Linear/ serpiginous/ stellate ulcers	+++	-
	Ulcers in terminal ileum	+++	-

Medical management

CROHN DISEASE

Induction of remission: Oral / i.v. glucocorticosteroids, oral glucocorticosteroids + azathioprine (AZA)/ mercaptopurine (6MP), or enteral nutrition.

Maintenance of remission: Aminosalycilates, or AZA + 6MP + mycophenolate mofetil.

Treatment of glucocorticosteroid/ immunosuppressive therapy-resistant disease: Methotrexate, i.v. cyclosporin or Infliximab (TNFα antibody)

Perianal disease: Ciprofloxacin and metronidazole.

ULCERATIVE COLITIS

Proctitis: Oral aminosalicylates and a local rectal steroid preparation are the first-line treatment. Mesalazine and budenoside enemas can be tried. In resistant proctitis, oral corticosteroids alone or in combination with azathioprine are used.

Left-sided proctocolitis: Oral aminosalicylates and a local rectal steroid preparation in mild disease. In moderate to severe attacks, oral prednisolone will be required.

Total colitis (moderate to severe attacks): Oral salicylates, i.v. hydrocortisone and full supportive therapy (i.v. fluids, nutritional support via the enteral and not parenteral route if required) +/- azathioprine. In patients responding to i.v. hydrocortisone treatment, oral prednisolone therapy should be substituted and doses slowly tapered.

Maintenance of remission is with aminosalicylates. When it is not possible to taper the dose of prednisolone without flare-up, azathioprine is used.

ASA compounds available for UC.

Drug	Preparation	Mechanism of release
Sulphasalazine	5- ASA linked to sulphapyridine	Bacterial cleavage in colon
Asacol (enteric-coated mesalazine)	5-ASA pH-dependent coating	Dissolves at pH 7 or higher
Salofalk (enteric-coated mesalazine)	5-ASA pH-dependent coating	Dissolves at pH 6 or higher
Pentasa (modified-release mesalazine)	5-ASA semipermeable membrane	Timed release of drug at luminal pH 6 or higher
Dipentum (olsalazine)	A dimer of two 5-ASA molecules, linked by azo bond	Colonic bacteria cleave azo bond
Colazide (balsalazide)	5-ASA linked to 4-aminobenzoyl-3-alanine	Colonic bacterial cleavage

Surgical management

Indications of surgery in CD and UC.

Crohn disease	**Ulcerative colitis**	
Failure of medical treatment Complications: Toxic dilatation Obstruction Perforation Abscesses Enterocutaneous fistulae Failure to thrive	*Fulminant acute attack*	Failure of medical treatment Toxic dilatation Hemorrhage Perforation
	Chronic disease	Incomplete response to medi- cal treatment Excessive steroid requirement Non-compliance with medica-tion Risk of colorectal carcinoma

Within 20 years of diagnosis, 80% of patients with Crohn disease require surgery, and many require multiple procedures. The surgical management of CD should be considered as a last resort and resections performed parsimoniously, since recurrence is inevitable (15% per year) with 20-30% of patients concerned within the first postoperative year.

In patients with ileal disease, some strictures are treated conservatively with stricturoplasty, however long or multiple strictures require resection and end-to-end anastomosis.

In total colonic involvement with rectal sparing/minimal rectal involvement, a subtotal colectomy and ileorectal anastomosis is performed. 2/3 of these patients are expected to experience recurrent ileal and/or rectal disease. 2/3 of these patients preserve a functional rectum for 10 years. In total colonic and rectal involvement, a panproctocolectomy with an end ileostomy is an obligate procedure.

While the treatment of UC remains primarily medical, its surgical management when needed is governed by the same conservative philosophy with which CD is approached.

Within 20 years of diagnosis, 1/3 of patients with UC will undergo colectomy and about 2/3 will require a second surgery.

In acute disease, subtotal colectomy with end ileostomy and preservation of the rectum is the procedure of choice. Later, either proctectomy with a permanent ileostomy or ileorectal anastomosis is performed. It is true that the latter procedure avoids a permanent ileostostomy and preserves the rectum, but perseverant surveillance of the rectal mucosa through annual biopsies must be achieved to exclude dysplasia, a precursor lesion for rectal stump carcinoma. An other alternative procedure is ileal pouch anal anastomosis (IPAA) with endoanal mucosectomy of the distal rectum and anal canal. While continence is usually achieved with this procedure, 1/3 of patients will experience pouchitis which presents with diarrhea, bleeding, fever and eventually exacerbation of extracolonic manifestations. In an attempt to ameliorate night-time continence, some surgeons advocate stapling the ileal reservoir to the distal rectum or proximal anal mucosa (ileal pouch-distal rectal anastomosis). The disadvantage of this technique is the cancer risk associated with diseased mucosa.

Colorectal carcinoma and IBD

The risk of development of colon carcinoma is estimated to be 20 percent/decade, after the first 10 years of UC. It is true that the incidence of carcinoma complicating CD is less than in UC, however the risk of colorectal carcinoma is still 20 times higher than in the general population. Many centers recommend that colonoscopy should be performed during the remission periods (to avoid iatrogenic perforation) at 1-3 - year intervals in patients with extensive UC of more than 10 years' duration, and multiple biopsies (2-4 biopsies/10cm, even more specimens are harvested from the left colon, and elevated, stenotic and ulcerated segments).There is insufficient evidence to support the use of a surveillance program in patients with CD.

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Correspondence to:
Mejdi Rachid
Calea Aurel Vlaicu st. N°6, Bl. A7 / C. Apt. 7
Arad 310141
Romania,
Email: mejdirachid@yahoo.com