Review

IBD: *Did you know...?*

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Inflammatory bowel disease (IBD) is a group of idiopathic disorders where the inflammatory cascade is activated, resulting in varying extent of inflammation within the bowel wall. Although, in theory, many disorders of the gastrointestinal tract could be considered under the heading of IBD, the term is typically used to refer to either Crohn's disease (CD) or ulcerative colitis (UC). A third, rarer type of IBD—microscopic colitis—also exists, though only CD and UC will be discussed in this summary article.

Etiology

The cause of both CD and UC is unknown. There are many theories regarding the etiology, most of them resting upon an antigen stimulating an immune response that cascades excessively within the gastrointestinal tract, resulting in bowel wall injury through inflammation.[1-4]

There have been several infectious antigens which have been considered as potential keys to the initiation of CD,[5-7] including:

- viral (measles, measles vaccine and reovirus),[8]
- atypical (mycobacterium paratuberculosis) and
- bacterial (cell-wall deficient pseudomonas).

In animal studies, within genetically susceptible hosts, a classic pathogen is actually not required to induce a chronic inflammatory response, which may instead result from nonpathogenic commensal organisms. This seems to implicate a certain genetic predisposition to development of the disease, which is supported by the fact that the relative risk of CD, among first-degree relatives, is approximately 14 times higher than the general population. It may well be that a genetic predisposition[9-12] is present in many patients—perhaps even a primary mucosal permeability defect[13]—and is exposed by an appropriate antigen, which produces an inflammatory response that, in some cases, may be exaggerated.[14]

The major advances in therapy rest upon understanding the inflammatory cascade that may be defective in some patients. The antigen is usually detected and initially managed through macrophages within the mucosal wall, where it is subsequently presented to T- and CD4-cells, leading to the latter's activation and differentiation into various types. Different factors—some pro-inflammatory, some anti-inflammatory—are subsequently produced, regulating the inflammatory response. Many of the newer therapies (*i.e.*, biological agents) target specific mediators of the inflammatory cascade.

In UC, there is also well documented genetic predisposition, with 20% of patients having a first- or second-degree relative affected with IBD. Perinuclear antineutrophil cytoplasmic antibodies are present in 75% of patients, supporting the autoimmune nature of this disease. Interestingly, smokers are less likely to develop UC, possibly through its effect on mucous production of the colonic mucosa.[15-18]

Pathology

There are several classical key differences between UC and CD, which are clearly demonstrated pathologically.

UC, by definition, is a disorder of the colon which typically results in mucosal inflammation extending proximally from the anal verge. In 20% of patients, the entire colon is affected (pancolitis), 30% have the disease extending proximal to the sigmoid colon and 50% have the disease affecting only the rectum (*i.e.*, proctitis) or rectosigmoid.

CD tends to cause focal intestinal inflammation and can occur at any site throughout the gastrointestinal tract. There tend to be interspaced segments of disease (*i.e.*, skip lesions) with transmural inflammation and the presence of granulomata usually differentiate it from UC. CD has a predilection for the terminal ileum, with 70% of patients having the disease at this site. About 50% of patients have the disease affecting both the ileum and colon, with one-third having disease isolated to the small intestine. CD can be classified by site (Table 1). In some patients, perianal disease may precede intestinal manifestations by many years.

Table 1

Vienna Classification of Crohn's disease[19]

Age at Diagnosis	A1, <40 year A2, ≥40 year
Location	L1, terminal ileum L2, colon L3, ileocolon L4, upper gastrointestinal
Behaviour	B1, nonstricturing, non-penetrating B2, structuring B3, penetrating

Table 2

Truelove and Witts' disease severity index[20]

Symptoms	Severity	
	Mild	Severe
Diarrhea	< four bowel movements/day	> six bowel movements/day
Blood in stool	Small amounts	Gross bleeding
Fever	Absent	Present
Tachycardia	Absent	Present
Anemia	Absent	Present
ESR	Normal	>30 mm/hour

Clinical presentation

Since UC affects the distal colon, presentation is usually with bloody diarrhea. The extent of inflammation tends to affect the severity of presentation. For example, if only the distal rectum is affected (*i.e.*, proctitis) then bright red blood per rectum may be the only presenting complaint. On the other hand, if the entire colon is diseased (*i.e.*, pancolitis) the patient may present with:

- bloody diarrhea,
- weight loss,
- fever,
- anemia and
- abdominal pain.

The grading scale for severity of disease by Truelove and Witts (Table 2) gives a good idea of the important clinical parameters to consider when assessing patients with this disease.

In contrast to those with UC, the presentation of CD may be subtle and varies considerably. Since any site of the gastrointestinal tract may be involved (from mouth to anus) the presentation tends to reflect the diseased segment. For example patients may present with perianal disease (*i.e.*, fistula, recurrent anal fissures or

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abscess) with primary complaints reflective of this region. Alternatively, in some patients, upper gastrointestinal involvement may even affect the esophagus with the presentation of dysphagia. To complicate matters, sometimes the inflammation is mild, producing complaints that are relatively vague or non-specific.

Since most patients with CD have disease affecting the terminal ileum, complaints reflective of this region are common. Obstructive symptoms (in stenosing disease) may result in:

- nausea,
- abdominal distention,
- pain and
- vomiting often with associated weight loss.

Diarrhea may also result from malabsorption of ileal contents. Patients with primary colonic disease may present similarly to those with UC. The Crohn's disease activity index (CDAI)[21-22] has been used to assess the activity of the disease and is usually used with studies to assess response to treatment.

The eight variables on the index include:

- the number of liquid/soft bowel movements during the previous week,
- the severity of abdominal pain/cramps,
- general well being,
- extraintestinal manifestations,
- the presence of an abdominal mass,
- use of antidiarrhea drug therapy,
- body weight and
- hematocrit.

These variables are combined and a score is produced. Patients in remission have scores of less than 150 on their CDAI.

Diagnosis

The diagnosis of both CD and UC rests on the appropriate history, which usually guides the investigations. Chronicity of symptoms is critical since other disorders (*i.e.*, particularly infectious causes of diarrhea) may cause similar endoscopic appearances as IBD. For patients suspected of having UC, a flexible sigmoidoscopy is usually diagnostic. The proximal extent of disease may not be visualized with a limited colonic examination and therefore, at a later date, a full colonoscopy may be required. There is no role for a barium enema in the diagnosis of UC.

CD can present with involvement throughout the gastrointestinal tract; therefore, the patient's presenting symptoms guide the investigations. Since 70% of patients have terminal ileal involvement, often this area is investigated first, with either a colonoscopy (with intubation of the terminal ileum) or a small bowel barium study. In both studies, classic skip lesions are characteristic of this disease.

Since some patients with CD can present with colitis, the distribution of the inflammation (*i.e.*, rectal sparing) and presence of perianal disease (fistula, fissure or skin tags) may be helpful in ascertaining the true underlying diagnosis. Other investigations may benefit certain patients: CT scanning to assess complications, such as abscess formation and capsule endoscopy for more sensitive visualization of the small intestine.[23]

Extraintestinal manifestations

There are several unusual extraintestinal manifestations of disease that occur that can even precede the diagnosis of IBD and may occur in up to 25% of patients with IBD. These disorders are usually immunologically based and often respond to treatment of the underlying condition. Arthritis, usually asymmetric involving one or more joint may result in significant disability. IBD is also associated with

ankylosing spondylitis.[25-25]

There are numerous eye manifestations, including episcleritis and scleritis, as well as skin manifestations, such as pyoderma gangrenosum and erythema nodosum, which may require involvement of other subspecialists for management. These conditions can also be found in disorders other than IBD so their presence does not preclude other diagnostic possibilities.

Gallstones are found in 25% of patient with CD. Sclerosing cholangitis occurs in both CD (usually in patients with colonic involvement) and UC.

Treatment

The primary goals of therapy must always be appreciated when treating UC and CD. Initially, in a patient with the active disease the primary goals of therapy are to induce remission and then to maintain it. In both disorders, the severity of the disease will guide the toxicity of therapy. For instance, those patients with very distal colitis (*i.e.*, proctitis) may simply require topical therapy in the form of enemas or suppositories. More proximal and severe disease will require escalation of therapy to systemic treatment.

UC

Sulfasalazine—the parent compound used in IBD—was coincidentally found to improve symptoms in those with colitis that were actually being treated for arthritis. The active component of this drug is the 5-aminosalicylate (5-ASA, or mesalamine), which together with sulfapyradine moiety, composes sulfasalazine. Since many of the untoward side-effects are secondary to the sulfapyradine moiety component, the mesalamine component has been isolated to minimize complications. Mesalamine has been further modified to enhance delivery to the distal intestine through either pH-dependent or delayed delivery so that the topical effect can be obtained in the diseased portion of bowel. Mesalamine compounds are effective for treatment and maintenance for mild to moderate UC, including left-sided disease that does not respond to topical therapy.

For those with moderate-to-severe disease, institution of immunosuppressive agents is required. This may include a course of corticosteroids (usually prednisone, at a dose of approximately 40 mg, tapering slowly over eight weeks) with or without the addition of azathioprine or 6-mercaptopurine (6-MP) which would be used on a long term basis.[27] The role of the corticosteroid is to induce the remission and the azathioprine/6-MP to maintain the remission thereby limiting further use of corticosteroid therapy.

For severe UC not responding to corticosteroid therapy, the use of intravenous cyclosporine has been demonstrated to be effective. This is usually in the hospitalized patient, administered by physicians with experience with immunosuppressive agents in a very select patient population. More recently, several studies have demonstrated the effectiveness of infliximab.[28] It appears to be effective in both inducing remission and maintaining remission in refractory cases. Further data and cost effectiveness will guide the use of this therapy however, for appropriate patients, this therapy, even though it is relatively expensive, will be used. In severe or refractory disease, surgical intervention in the form of a colectomy is always considered. There are several options of surgical intervention, one of them being proctocolectomy with ileoanal pouch formation.

CD

With the advent of new modalities of therapies the management of CD has become more complex. For patients with mildly active disease, 5-ASA compounds have traditionally been used with modest

benefit in studies. For maintenance, particularly in ileal disease (the most common site of disease), their role is limited, as their benefit in prevention of further exacerbations is marginal. For acute exacerbations of moderate-to-severe disease the use of corticosteroids has proven to be of benefit in inducing remission; however, because of an unfavorable long term side effect profile, there is no role for long-term steroid therapy. To avoid the side-effects of corticosteroid therapy, budesonide has been developed which has limited systemic complications. Unfortunately, its benefit—outside of induction in remission—is questionable and therefore, not usually used long-term to prevent exacerbations.

Although induction of remission may be possible with the agents noted above, the patient with frequent exacerbations requires intervention to prevent recurrences. For this purpose, the use of immunosuppressive agents (imuran/6-MP/methotrexate) have been used with proven benefit. Generally, these agents elicit their effect over a period of weeks and are designed (if tolerated) to be taken for months to years (*i.e.*, long-term therapy).

The use of antibiotic therapy is occasionally beneficial for patients with active CD; however, proven benefit has been primarily in those with distal/perianal disease.

The recent development of newer agents with targeted immunosuppressive activities has stimulated a new era in therapy of IBD. Infliximab is an anti-tumor necrosis factor (TNF) agent, with well-documented benefit in most areas of active CD for induction as well as maintenance of remission.[29-30] The development of antibodies to infliximab, resulting in both allergic reactions and loss of response, has stimulated testing of "humanized" anti-TNF products.[31-32] Other biological agents are also under investigation[33-34] and will be approved for therapy in the near future. These agents tend to be relatively expensive; however, for select patient populations that require significant resource utilization, their benefit (even from a cost point-of-view) is clear.

The treatment of IBD appears to be undergoing major changes and over the next several years, newer agents will dominate the therapeutic armamentarium of the physician. These agents will have their own drawbacks, but hopefully, will enable those patients with difficult-to-control disease to resume a more normal lifestyle and take us one step closer to a cure for these disorders. Dx

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