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Clinical Features and Treatments of Inflammatory Bowel Disease (IBD) – An Update

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Clinical Treatments and Features of Inflammatory Bowel Disease (IBD) – An Update

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The approach to IBD (inflammatory bowel disease) has changed considerably over the past few years as our understanding of IBD pathophysiology, particularly the immunological basis of disease, has improved.

Nearly two million people are affected with IBD [e.g., Crohn's disease and ulcerative colitis] in the U.S. These inflammatory conditions are a group of several disorders, in which the extent and activity of inflammation within the gastrointestinal (GI) tract may be quite diverse. The age of onset is usually in the 20s and 30s, although there is a slight second peak in incidence in the 50s to 60s. Men and women are equally affected in IBD as opposed to IBS, which is female predominant. There appears to be a genetic predisposition to the development of IBD: nearly 10 percent of patients with IBD have a first-degree relative with IBD. A Crohn's disease susceptibility gene (IBD1), which codes for a molecule responsible for binding bacterial pathogens in the cell (NOD2), is mutated in up to one-quarter of all Crohn's disease (CD) patients. This and other observations lead to the current concept of impaired tolerance to one's own gut bacteria as the pathogenic mechanism of IBD.

Interestingly, research has also begun to shed light on findings that chronic stress can result in an altered immune response, which may manifest as a spectrum of GI abnormalities, from Irritable Bowel Syndrome, IBS, (where minimal inflammation is seen on endoscopy) to IBD (where inflammation and ulceration are apparent upon these examination). It is thought that corticotrophin – releasing factor, a chemical mediator of stress response in the brain, activates receptors (molecules) in the gut by working through a complex neuronal pathway, which, in turn, results in inflammatory changes of gut mucosa (gut lining). These changes cause such symptoms as abdominal bloating, flatulence, abdominal pain and altered bowel habits. Research suggests that a chemical serotonin plays an important role in mediating these sensations in susceptible patients.

It is often difficult to distinguish between IBD and IBS solely based on symptoms, as they often overlap. In fact, some investigators believe that there may be a common genetic predisposition that contributes to enhanced responses to life stress via alteration of neuronal pathways with resulting effects on susceptibility to gut infections. Endoscopic examination is often required to distinguish between IBD and IBS. Recently, researchers discovered stool markers (chemicals found in stool) that are able to

differentiate between IBD and IBS. These markers (lactoferrin and calprotectin) are proteins derived from leukocytes (white blood cells) in the colonic lining and therefore reflect the amount of inflammation in the colon. Tests measuring lactoferrin and calprotectin (PhiCal Test and IBD-SCAN Test respectively) were found to be 90% accurate at distinguishing between IBD and IBS. In addition, fecal calprotectin and lactoferrin correlated with endoscopically assessed disease severity in IBD.

Ulcerative Colitis (UC)

UC occurs when the large intestine becomes inflamed with superficial ulcerations. These ulcerations usually begin in the rectum and spread towards the cecum (end portion of colon). The hallmark symptoms are diarrhea associated with blood and mucus. If inflammation involves just the rectum (proctitis), then urgency and *tenesmus* (painful bowel movements) may be the only sign of rectal inflammation. Nearly 30% of patients with ulcerative colitis begin with proctitis. This condition tends to run a benign course and is usually not associated with manifestations outside the intestines. As the colon becomes more inflamed, anemia and other non-colonic symptoms may occur (e.g., erythema nodosum, uveitis, and arthritis).

Crohn's Disease (CD)

This inflammatory disorder may involve the entire gastrointestinal tract from mouth to anus. Inflammation is usually not confined to the superficial lining of the GI tract but can involve the entire wall thickness (transmural). Areas of normal colonic mucosa are usually seen interspersed with areas of inflammation. The ileocecal area is affected in 40–50% of patients, while the small intestine is affected in 20–30%, and colon only in 20% of patients. Most patients have either *ileitis* [inflammation of the ileum] or *ileitis* with coexistent *colitis* [inflammation of the colon].

Serologic Markers

In addition to the clinical course, endoscopy, x-ray, and biopsy findings, new blood tests (serologic markers) have become available to the clinician. These markers can be used to help differentiate between CD and UC, predict IBD risk before symptom onset, predict therapeutic efficacy of some medications and monitor response to therapy. These markers are generally cheaper and less invasive than endoscopy with biopsy; however, at this point in time, none of the markers can be used as stand – alone tools for diagnosing and prognosticating IBD. Five biomarkers have been most widely studied: ASCA (anti-saccharomyces cerevisiae antibodies), pANCA (perinuclear antineutrophil

cytoplasmic antibodies), anti-OmpC (antibodies against bacterial outer membrane porin C), anti-I2 (antibodies against *Pseudomonas fluorescens* bacterial sequence) and anti-CBir1 (antibodies against bacterial flagellin). In addition, three new anti-carbohydrate antibodies have been discovered (ACCA, ALCA, and AMCA). Together, they complement ASCA in discriminating between CD and UC. ASCA is specific to Crohn's disease (detected in 50 – 70% of CD patients), is associated with more aggressive small bowel disease and the need for small bowel surgery, and predicts response to infliximab and other anti – TNF therapy. Perinuclear ANCA is more specific to UC (found in 50 – 60% of UC patients), but can be found in CD patients whose disease involves the colon. CBir is found in 50% of patients with CD and serves as a marker of colonic disease in children and small bowel disease in adults. Combinations of more than one of the 5 serologic markers have been shown to have the most value in differentiating between UC and CD and predicting disease location and severity. Thus, the more antibodies an individual has, the lower the level of one's immunity and the higher the risk of having more complicated Crohn's disease. No similar association was found for UC at this time.

Treatment of Inflammatory Bowel Disease

Treatment of IBD is aimed at decreasing the inflammatory response seen within the GI tract and thereby improving the patient's symptoms.

5-ASA Preparations: Oral derivatives of 5-ASA (sulfasalazine, Asacol®, Dipentum®, Pentasa®, Colazal®, Lialda®, and Apriso®) are generally efficacious for either the induction and/or maintenance of remission in mild to moderately *proctitis* [inflammation of the rectum], left sided colitis, or *pan-colitis* [involving the entire colon]. Different mechanisms of release of mesalamine, the active ingredient, allow each preparation to be delivered to a specific site in the GI tract. Lialda® and Apriso® are the newest 5-ASA agent with a slow release formulation, which makes it a once daily drug. The available evidence does not support the use of 5-ASA agents as maintenance therapy in CD; however, 5-ASA compounds are still being prescribed by many physician for CD. One of the reasons may be that 5-ASA compounds appear to reduce the risk of colon cancer (serve as chemoprevention) in patients with long standing colitis. Recent evidence suggests that higher doses than previously used may be employed to achieve full effect of 5-ASA compounds (up to 4.8 grams daily). Side effects may include nausea, headaches, fever, and hypersensitivity reactions.

Steroids: If the 5-ASA products are not controlling colitic symptoms, a physician may add steroids (e.g., prednisone, Deltasone, dexamethasone, IV hydrocortisone) to induce remission of moderate to severe colonic inflammation. However, steroids have not been found to maintain remission in either UC or CD. The side effects of prednisone such as mood swings (euphoria/depression),

hypertension, osteoporosis, aseptic necrosis of the hip, diabetes, adrenal suppression, and cushingoid features just to name a few, have limited its long-term use.

Budesonide is a steroid with limited systemic availability due to its high rate of metabolism by the liver upon ingestion. It is released in the ileum and right colon and is therefore generally used in CD and right sided UC. Although short-term efficacy with budesonide is less than with conventional steroids, particularly in patients with severe disease or more extensive colonic involvement, the likelihood of adverse events is lower. Budesonide is not recommended for maintenance of remission in Crohn's disease due to poor efficacy and unfavorable side effect profile.

Immunosuppressants/Immunomodulators: The *thiopurines*, 6-mercaptopurine (6-MP) and its prodrug, azathioprine (AZA) have been used for over 30 years in adults with IBD. These medications have been shown to be effective for inducing and maintaining remission in CD and UC. Additionally, AZA and 6-MP, taken together with an antibiotic Flagyl, have been shown to reduce recurrence of CD after surgery (ileocolonic resection). The onset of action is slow (greater than 3–6 months). Side effects may include *myelosuppression* [suppression of the bone marrow's production of blood cells and platelets], hepatitis, pancreatitis, and infection. Monitoring blood counts to avoid *leucopenia* (decreased white blood count) is important. Recently, the measurement of an enzyme, TPMT, which is involved in the breakdown of the thiopurines, has been helpful to determine the dosage of 6-MP and AZA. Patients with low enzyme activity are at risk for higher side effects such as bone marrow toxicity.

Methotrexate (MTX), a competitive antagonist of folic acid which interferes with DNA synthesis, has been shown to induce and maintain remission in steroid dependent patients with Crohn's disease. A double blind control study did not show the same efficacious effect with ulcerative colitis patients. This medication should not be used in pregnancy.

Cyclosporine: Cyclosporine is a potent fungal compound, which has many effects on altering the immune system. It is used to prevent colectomy and induce remission in severe UC patients not responding to steroids. It is not used to maintain long term remission. Side effects such as *nephrotoxicity* [kidney damage], hypertension, seizures, mild *encephalopathy* [dysfunction of the brain], and *paresthesias* [abnormality of sensation, such as tingling or numbness] have been reported. CSA has not been found to be as effective in treating CD.

Anti-TNF antibody – the future of IBD therapy: The development of a monoclonal antibody to tumor necrosis factor alpha has proven to be effective for treatment of patients with moderate to severe Crohn's disease who have not responded to conventional therapy. A number of TNF alpha inhibitors have been developed and approved by the FDA to induce and maintain clinical remission in Crohn's

disease. Infliximab (Remicade®) is an antibody of mouse origin administered as an intravenous infusion, which has been found to be superior to placebo for induction of remission (about 40% response rate in patients with moderate to severe Crohn's disease), maintenance of remission in patients who responded to the initial induction dose, closure of draining enterocutaneous fistula and corticosteroid sparing. Adalimumab (Humira®) is an antibody of human origin administered subcutaneously, which has been found to have similar rates of induction and maintenance of remission, fistula closure and steroid sparing as Infliximab®. Certolizumab® is a humanized antibody fragment with a long half life administered subcutaneously, which has been shown to have a modest improvement in the initial clinical response but no long term improvement, as compared with placebo, in patients with moderate-to-severe Crohn's disease. CDP571 is an antibody of mouse origin, which has not been found effective for maintenance of remission in patients with Crohn's disease. Of the four anti-TNF alpha agents, Infliximab® is the only one which has been evaluated for treatment of Ulcerative colitis. It has been shown to be effective for treatment of moderate to severe UC and is recommended for patients who have had an inadequate response to medical therapy or who are unable / unwilling to tolerate side effects of other agents, such as immunomodulators. Finally, anti-TNF alpha agents have been found efficacious for treatment of extraintestinal manifestations of IBD (pyoderma gangrenosum, uveitis, ankylosing spondylitis). Lymphoma risk in patients undergoing anti-TNF alpha therapy is controversial, the absolute risk remains very low. Overall infectious rates have been shown to be similar between patients receiving anti-TNF agents and placebo.

Probiotics: Probiotics are microbial preparations that contain live and dead bacteria. Recently, a probiotic (VSL#3®), which includes 8 different bacterial species, has been shown to prevent and treat chronic *pouchitis* (inflammation of internal ilial pouch) in postoperative patients. Another probiotic strain, *E. coli Nissle*, has been shown to be as efficacious as low dose 5-ASA compounds in maintaining remission in mild UC. Probiotics are also beneficial in antibiotic-associated diarrhea. There has been no evidence to suggest benefit in CD.

Prebiotics: Prebiotics are substances that support beneficial bacteria. They include lactulose, fructo-oligosaccharides, fatty acids and fiber. They have been shown to work for *Clostridium difficile* infection of the colon and small intestine. The available data from properly designed studies are insufficient to draw conclusions about the effects of Omega-3 fatty acids or dietary fiber on remission and relapse rates in IBD, although some reports of efficacy of the above interventions exist.

Biotics: Biotics are live organisms ingested and maintained in the GI tract, such as helminthes. Helminthes are powerful stimulators of cytokine responses (chemical

responses) that suppress inflammatory responses implicated in IBD. However, biotics are *not* FDA approved at this time.

It is becoming more apparent that the relationship between gut flora and the gut immune system will become the focus of mechanism – based therapy in IBD in the future.

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Additional Resource

Crohn's and Colitis Foundation (CCF) website at www.ccfa.org

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