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Crohn's Disease: A Literature Review

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Abstract: ***Crohn's disease is a chronic relapsing inflammatory bowel disease that may affect any part of the gastrointestinal tract. The ileum, colon, and perineum are most commonly affected. It is characterised by transmural inflammation, and granulomata may be present. Whilst the aetiology of Crohn's disease is not completely understood, it is thought to be caused by the complex interplay between genetic, immunological, microbiological, and environmental factors. It is multisystem disorder with potential for systemic and extraintestinal complications can affect any age group, but the onset is most common in the second and third decades. The most common symptoms of Crohn's disease are diarrhoea, abdominal pain, weight loss, and fatigue. Symptoms reflect the site and behaviour of disease, and the presence or absence of strictures and fistulae. Treatment has changed radically over the past decade with the introduction of biological therapy and increased use of immunomodulators. Awareness of the therapeutic potential and associated adverse events is necessary both for offering benefit and for protecting patients from undue risks from these treatments.***

Keywords: Crohn's disease, diarrhea, ileum, immunomodulators

1. Introduction

Inflammatory bowel disease (IBD) is a group of disorders that causes sections of the gastrointestinal tract to become severely inflamed and ulcerated. An abnormal response of the body's immune system plays a role in each of the two main forms of IBD; namely Crohn's disease (CD) and ulcerative colitis (UC). IBD has a tremendous impact on quality of life due to a host of devastating symptoms, as well as a substantial personal burden. Crohn's disease encompasses a multisystem group of disorders with specific clinical and pathological features characterized by focal, asymmetric, transmural, and, occasionally, granulomatous inflammation primarily affecting the gastrointestinal (GI) tract.

Crohn's disease can cause significant morbidity with symptoms including abdominal pain, diarrhoea, faecal incontinence, rectal bleeding, weight loss, and fatigue. The prevalence is increasing in both the West and in the developing world. Crohn's disease particularly affects young adults at a time in life when they are in education, starting work or family lives, and it can have a major impact on quality of life.

CD is a chronic in ammatory disorder that is neither medically nor surgically "curable," requiring therapeutic approaches to induce and maintain symptomatic control, improve quality of life, and minimize short- and longterm toxicity and complications [2]. Newer goals of therapy include the induction and maintenance of mucosal (and histologic) healing [3, 4] that are beginning to translate into changing the " natural history " of CD [5].

Aetiology
The aetiology of Crohn's disease is incompletely understood. It is known that immunological, microbiological, lifestyle, and genetic factors are implicated.

Genetics
Family history is a major risk factor for Crohn's disease. Having a first degree relative with the disease increases the risk 10-fold; and 9-15% of patients with Crohn's disease have an affected first degree relative. The highest risk is with monozygotic twins, where disease concordance is between 35-50%.[6]

Immunology
Mutations at gene loci coding for immune molecules and pathways, identified via GWAS, have implicated a range of immunological 'culprits' involved in the pathogenesis of Crohn's. Defects in both the innate and adaptive immune systems are present in Crohn's disease. Barrier function, the first line of innate defence, is impaired by both an inadequate mucous layer, and by abnormally low levels of protective antimicrobial peptides, which admit greater antigenic and microbial exposure to the epithelium.[7]

2. Environmental Factors

Smoking
Smoking is an independent risk factor for developing Crohn's disease, and has been widely studied. For patients with Crohn's disease, smoking increases progression to more advanced disease (stricturing and/or penetrating); and cessation of smoking is associated with a reduction in progression to advanced disease, and a reduced need for surgery.[8]

Diet
Since diet provides the bulk of the antigenic stream that passes through the intestine it would seem likely that dietary factors are relevant in the aetiology of Crohn's disease. However, no food component has yet been proven to be clearly implicated in the pathogenesis. Elemental and polymeric diets, both with lower antigenic load than a normal diet, are successful treatments for Crohn's disease in children. A recent large population-based study has shown that high intake of long chain 3-PUFA may be protective against ulcerative colitis, whilst high intake of transunsaturated fats may predispose to disease. The data were not significant for Crohn's disease.

Microbiome
The microbiome consists of billions of microorganisms that line the intestinal mucosa. The composition of the flora within the microbiome is affected by host and environmental factors. The converse is true also, with the microbiome able

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to alter mucosal cell DNA sequences. The sheer size of the microbiome, together with its important symbiosis with intestinal immunity, has led to some observers calling the microbiome an organ in its own right. Modern techniques, especially high resolution mass spectroscopy and nuclear magnetic resonance, have enabled detailed study of the constituents of the microbiome.

Symptoms

Persistent diarrhea, crampy abdominal pain, fevers, and, at times, rectal bleeding are the hallmark symptoms of CD, but they vary from person to person and may change over time. Loss of appetite and subsequent weight loss may also occur. However, the disease is not always limited to the GI tract; individuals may experience symptoms outside of the intestine, which may affect the joints, bones, eyes, skin and liver. Fatigue is another common complaint. Children who have CD may suffer osteoporosis, and may fail to develop or grow properly. Some patients may develop tears in the lining of the anus, which may cause pain and bleeding, especially during bowel movements. A fistula is a tunnel that leads from one loop of intestine to another, or that connects the intestine to the bladder, vagina or skin. Fistulas occur most commonly around the anal area. If this complication arises, the patient may drain mucus, pus, or stool from this opening.

Management

Therapeutic goals include: induction and maintenance of clinical and endoscopic remission, swift resolution of exacerbations, maintenance of adequate nutrition, regular surveillance for complications, monitoring for and avoidance of adverse drug-induced effects, and optimising quality of life. A distinction must be made between inducing and maintaining remission. Patient education is increasingly recognized to improve compliance with therapy.

Smoking Cessation

Cessation of smoking is an effective intervention in the treatment of Crohn's disease. Smoking predisposes to a more aggressive disease course, with stricturing and fistulising disease.[8]

Diet

Polymeric and elemental diets are effective at inducing remission in children, but less so in adults.[9]This may relate to compliance. A low residue diet helps prevent sub-acute bowel obstruction in patients with stricturing disease.

Aminosalicylates

Published meta-analyses are inconsistent with regards to efficacy of 5-ASA in Crohn's disease. European guidelines are that 5-ASAs are not recommended for maintenance of medically-induced remission of Crohn's disease.33 Sulphasalazine may be used for mild colonic disease and may be used in patients with joint symptoms. There may be a role for mesalazine in prevention of recurrence of post-operative Crohn's.[10]

Corticosteroids

Budesonide is first-line therapy for inducing remission of mild exacerbations of ileocaecal Crohn's disease. It is associated with fewer adverse effects than systemic steroids such as prednisolone. Systemic steroids can be used for inducing remission during severe flares of ileocolonic Crohn's disease, [10] but anti-TNF drugs may be more appropriate. Steroids are not safe or efficacious for maintenance therapy.

Antibiotics, Probiotics, Prebiotics, and Faecal Transplantation

Ciprofloxacin and metronidazole are effective for treating septic complications of Crohn's disease and for perianal disease. The long-term sequelae of these two drugs include Achilles' tendon rupture and peripheral neuropathy, respectively. There is no convincing evidence that antibiotic therapy is effective in maintaining remission in Crohn's disease.

Immunomodulators

The thiopurines azathioprine and 6-mercaptopurine are widely used to maintain medically induced remission of moderate-to-severe Crohn's disease. Onset of action is slow, and full clinical response may take up to 16 weeks, therefore immunomodulators should not be used as single agent therapy, but should be used alongside a drug that induces rapid remission.

Anti-TNF Therapy

Monoclonal antibody therapy, including infliximab, adalimumab and certolizumab, is effective for induction and maintenance of remission of moderate-to-severe Crohn's disease. Development of antibodies to the drug may impair efficacy, but incidence of antibody formation can be reduced by regular scheduled dosing (as compared with ad hoc dosing) and by concomitant use of an immunomodulator.[11]

Surgery

Distal ileal resection can be considered for short segment moderate-to-severe disease. Extensive small bowel resection can lead to short bowel syndrome, and so intensification of medical therapy and trial of stricturoplasty are important to attempt to maintain bowel length. Surgery is also performed for perianal complications and includes laying open fistulae and seton insertion as well as drainage of abscesses.

3. Conclusion

Crohn's disease is a chronic, relapsing and remitting inflammatory condition of the gastrointestinal tract. Treatment has changed radically over the past decade with the introduction of biological therapy and increased use of immunomodulators. Awareness of the therapeutic potential and associated adverse events is necessary both for offering benefit and for protecting patients from undue risks from these treatments.

4. Conflict of Interest

None declared.

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5. Sources of Funding

Nil.

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