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# Introductory Chapter: Crohn's Disease - Recent Advances

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## 1. Introduction

Crohn's disease and ulcerative colitis are the two main forms of inflammatory bowel disease (IBD). While ulcerative colitis mainly causes mucosal inflammation of the rectum and the colon, Crohn's disease is characterized by transmural inflammation of the gastrointestinal tract anywhere from the mouth to the anus and granuloma formation in about 30% of cases. Crohn's disease can also cause deep ulcers, penetrating ulcers, stricture, fistula, abscess, perforation, malabsorption and perianal disease. Although both forms of IBD can cause extra-intestinal manifestations and malignancy, Crohn's disease is, in fact, a much more severe disease and patients' sufferings can be relentless if the disease is not under control. The natural course of Crohn's disease is chronic inflammation with relapse and remission. As it affects mostly young population in the 20s and 30s, their prime time of life is hampered. So patients suffering from Crohn's disease always want to avoid any relapse and be in long-term remission. The exact etiology of Crohn's disease is unknown. Genetics, environmental factors (smoking, anxiety, depression, stress) and altered gut microbiota play important roles in disrupting the immune homeostasis that results in uncontrolled inflammation of the gut. A systematic review found that the prevalence of Crohn's disease was 319 cases per 100,000 people and the annual incidence was 20.2 cases per 100,000 persons-year in the United States [1]. It is more commonly seen in the white population in the Western world, but any person of any ethnicity can be affected. It is slightly more common in females than in males. The incidence and prevalence of Crohn's disease have been increasing globally. Kochar et al. found that United States born Asians and Asian immigrants suffer from more perianal and ocular Crohn's disease compared with white Americans [2].

There are various laboratory, imaging and endoscopic studies available to diagnose and assess the severity of Crohn's disease. Crohn's Disease Activity Index (CDAI) and Harvey-Bradshaw Index (HBI) are commonly used to assess the activity of the disease. Classically, Crohn's disease is divided into mild, moderate and severe disease. There are various immunomodulatory [6-mercaptopurine (6-MP), azathiopurine (AZA), methotrexate (MTX), and janus kinase (JAK) inhibitors] and biologic agents (anti-tumor necrosis factor, anti-integrin, IL-12/IL-23 inhibitors and biosimilars) available at the present time for induction of remission and maintenance of remission of Crohn's disease. Mild Crohn's disease is generally treated by a short course of budesonide followed by maintenance with 6-MP, AZA or MTX. Moderate to severe disease is treated with systemic corticosteroid followed by biologic agents with or without immunomodulatory agents. Primary non-response and secondary loss of response to the biologic agents and immunomodulators are not uncommon. These unfavorable outcomes can be evaluated by therapeutic monitoring of trough levels of drugs, measuring anti-drug antibodies (for anti-TNF agents) and metabolite levels (for thiopurines) so that appropriate management strategy

can be taken [3]. The goal of treatment is not only clinical and endoscopic remission but also mucosal healing. Although many patients are able to maintain long-term remission, the treatment options are not optimal considering their efficacy rate and side effect profile. As a result, many clinical trials are ongoing for better control of Crohn's disease. Many biologic agents are in the pipeline to be released into the market. Many patients ultimately need surgery when medical therapy fails and when complications occur. Fortunately, the surgery rate in Crohn's disease is decreasing. A population-based time-trend analysis showed that the incidence rates for surgery in Crohn's disease had been decreasing by about 8.4% each year from 1996 to 2013 [4]. Unfortunately, surgical intervention is not curative and patients still need to be on immunosuppressive or biologic agents to prevent recurrence of the disease. Preventive care is an important aspect of management of Crohn's disease. Because of immune dysregulation, patients are at increased risk of developing various viral and bacterial infections. They should be immunized against pneumococcus, meningococcus, mumps, measles, rubella, diphtheria, tetanus and varicella zoster virus. They are also prone to develop osteopenia, osteoporosis and deficiency of iron, vitamin and micronutrients. Baseline bone densitometry should be done, and calcium, vitamin D, iron, vitamin B12, folic acid and fat-soluble vitamins supplementation should be considered. Patients with Crohn's disease are also at risk of developing of skin cancer (melanoma and non-melanoma). Thiopurines increase the chance of developing non-melanoma skin cancer and there is an increased risk of developing melanoma after using biologic agents (anti-TNF, anti-integrin). Patients should avoid sun exposure by using sunscreens and annual skin cancer surveillance should be done by the dermatologist. Patients with perianal Crohn's disease are at increased risk of developing Human Papilloma Virus (HPV)-related anal canal squamous cell cancer and very rarely anal canal adenocarcinoma. They should receive HPV vaccination to reduce HPV-related malignancy. Female patients with Crohn's disease on immunomodulators or biologic agents have increased risk of developing cervical high-grade dysplasia/cancer. They should have regular PAP smear to prevent cervical neoplasia. Female patients with Crohn's disease in remission have the same chance of having conception, normal pregnancy and delivery as normal women without Crohn's disease. Pregnancy can have beneficial effects on Crohn's disease such as less symptoms during pregnancy, less future flare up and less need of future surgery. But if the disease is active, the chance of becoming pregnant is much less. Active disease during pregnancy can cause miscarriage, premature delivery and stillbirth. Thiopurines and anti-TNF agents are safe to be used throughout the pregnancy, and breastfeeding is also compatible with both agents. Methotrexate is teratogenic and cannot be used during pregnancy or lactation. In fact, both man and woman should stop taking MTX 3 months prior to planned pregnancy [5].

Taking care of mental health is another important part of management of Crohn's disease. Patients may suffer from anxiety, depression and narcotic related problems. Various factors may contribute to psychiatric comorbidity which include pain, insomnia, psychosocial stress, frequent hospitalizations, surgical procedures, presence of ostomy, history of proctocolectomy, long duration of Crohn's disease and history of traumatic childhood experiences [6]. During each outpatient visit, patients should be asked about their mental and emotional wellbeing, and appropriate referral to the psychologist or psychiatrist should be given.

In conclusion, Crohn's disease is primarily an idiopathic chronic inflammatory bowel disease with the potential of involving multiple organs. Benign and malignant complications as well as psychiatric comorbidity can occur. Management of Crohn's disease may require multi-specialty team that include primary care physician, gastroenterologist, surgeon, dietitian, interventional radiologist, obstetrician, gynecologist, oncologist, dermatologist, psychiatrist and psychologist. Preventive

healthcare and mental healthcare are also very important part of management of Crohn's disease. There are many support groups available in national organizations in individual countries such as Crohn's and Colitis Foundation of America, National Association for Colitis and Crohn's Disease in the United Kingdom, and Crohn's and Colitis Australia. Patients with Crohn's disease should join these support groups where they can communicate, find emotional supports, get answers to their questions and share their experiences with others living with the same disease.

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