INFLAMMATORY BOWEL DISEASE

Morten H. Vatn[1,2] and Arne K. Sandvik [3,4,5]

1. Instutute of Clinical Medicine, Campus Ahus, University of Oslo, Norway

2. Department of Transplantation and Cancer, Section of Gastroenterology, Oslo University Hospital, Rikshospitalet

3. Department of Gastroenterology and Hepatology, St. Olav's University Hospital, Trondheim, Norway

4. Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway

5. Centre of Molecular Inflammation Research, Norwegian University of Science and Technology, Trondheim, Norway

Corresponding author: Morten H. Vatn, MD. Prof., Institute of Clinical Medicine, University of Oslo, e-mail: m.h.vatn@medicine.uio.no

Abstract

Scandinavian reasearchers have contributed to the present understanding of inflammatory bowel disease (IBD). Important epidemiological data and family risk factors have been reported from all the Nordic countries, original twin studies mainly from Denmark and Sweden, and relationships to cancer and surgery mostly from Sweden. In collaboration with the industry, development of medical compounds was for a long time in the front line of international research, and the Scandinavian countries participated in the clinical break through of biologic treatment.

At present, many Nordic centres are working in the forefront of IBD research. An increasing number of young investigators have entered the scene along with the extended distribution of University clinics and research laboratories in these countries.

This presentation of IBD gives a brief overview in the fields of clinical epidemiology and molecular biology. Many areas are covered by International collaborations with partners from Nordic centres.

IBD was a topic focused by the founders of Scandinavian Journal of Gastroenterology. After 50 years one may state that the journal's history reflects important pieces of scientific knowledge within these diseases. The early scope of Johannes Myren for IBD was shown through his work in the original World Association of Gastroenterology(OMG), and after 50 years we can clearly support the view that global perspectives in IBD are increasingly important.

Introduction

The inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease, are chronic diseases occurring in genetically susceptible individuals exposed to environmental risk factors (1-3). In spite of extensive studies during the last decades, etiology and disease pathogenesis are not fully understood (1). CD peaks between 15 and 25, and UC between 25 and 35 years of age, followed by a life long   burden of diseases, in which reduced overall survival is questionable (4,5). Young age at onset is associated with complicated disease and reduced QoL (6), which calls for immediate and long-term demands for health-care resources. Time from onset of symptoms to diagnosis is usually less than 1 year both in adults and children (7,8) but may extend to several years. Time lag of diagnosis may affect response to treatment, and early irreversible changes may occur before medication is induced, whereby the patient might be primarily refractory to treatment.

Most IBD cases seem to be classified as UC or CD within 5 years after diagnosis (9). Because of continuous changes in treatment strategies, it is difficult to compare the disease course between past decades. Nevertheless, one might suspect a shift toward milder disease in UC related to a markedly reduced need for surgery (10) compared with previous experience. This reduction has not been observed over the long term in CD (11). Disease course depends on choice of treatment, but some features seem partly unrelated to conventional treatment, such as change in disease distribution, tendency of relapse, tendency of reoperations, and secondary fistulas.

Sulphasalazine, a drug of Scandinavian origin, was the first compound found to be effective in the control of UC (12). Today, limitations of 5-aminosalicylates and side effects of corticosteroids have led to use of immunomodulators such as azathioprine, or anti-TNF agents(13). Despite advances in medical treatment, surgical options are still needed for many patients. Ulcerative colitis is a surgically "curable" disease and approximately 25-30% of patients may require operative management usually in an elective setting(14). Surgery for Crohn disease (up to 80% of patients) is most commonly performed for complications of the disease (strictures, fistulas). Conservative resection is now advocated to preserve bowel length in case additional surgery is needed in the future (15).   IBD carries an increased risk of malignancy (16,17,18) and

may warrant endoscopic surveillance during long term follow up and early surgery. Possibly due to a more effective anti-inflammatory treatment, a lower IBD cancer risk has been reported recently (19). The cancer risk in primary sclerosing cholangitis is of particular interest, as this disease is not uncommon in UC and predisposes for both colorectal and biliary tract malignancy (20).

In polygenic diseases like IBD, a combination ofgenetic and environmental factors seem important for development of disease. In the present review, focus of relevans for mechanisms of disease and handling of patients are addressed

Epidemiology and genetic factors

Incidence and prevalence of IBD show great variations around the world, with associations to industrialization, with the highest incidence rates of IBD in North America and Europe including the Nordic countries (21,22,23,24).

In western countries, a suggested plateau level or even decline in incidence in certain geographic regions have been reported (25,26).

Recent reviews describe incidence and prevalence of IBD on a global basis (27,28,29). A north-south gradient for incidence rate, phenotype, and recurrence was demonstrated in Europe (21,30) and an east-west gradient in Canada (31).-Females are overrepresented in CD and males in UC. Several studies have demonstrated male predominance in children at a lower age and female predominance from puberty (7,32).

A high frequency of concordant disease among monozygotic twins has been demonstrated in CD (33). Having a family member with IBD is a risk factor. Familial cases are younger at diagnosis compared with sporadic ones, ascribed to genetic anticipation (34), and a relationship to disease outcome and severity has been suggested (35). The interplay between genetics/inheritance and environment by epigenetics, may clarify the natural history of individual disease (36). The NOD2 mutation seems to play an important role in the determination of disease phenotype, mostly related to ileal and fibrostenotic disease (37). None of the large number of genetic loci discovered

for CD in recent years was associated with a specific clinical phenotype. Nevertheless, the genetically determined innate immune system is pivotal for disease activity of an individual. The innate and acquired immune systems represent putative targets for early individual treatment strategies related to gene signaling at different levels, cellular immunity, antigen presenting molecules, epithelial integrity, drug transporters, and cell adhesion (38). CD is generally considered to be more genetically disposed than UC, however, the recently demonstrated defective interleukin-10 function, seems to suggest that genetic susceptibility is important for the development of UC (39), and like in CD(33), increased concordance rates among monozygotic twins has been demonstrated for UC (40). Molecular investigations have shown that Card15/Nod2- gene variants are associated with familial occurrence and complicated forms of CD (41). Moreover, increased relapse rate along with increased concordance of disease have been shown for first degree relatives of patients with UC (42). Altogether, a growing litterature tends to support a relationship between CD or UC and complicated disease in familial IBD. The observations of concordance for site and type of CD (43) and the influence of age at onset to phenotype (44)   have now been confirmed by genotyping. Moreover, the prediction of "genetic anticipation" in CD (45) has now been confirmed in a recent prospective follow up study of parent child pairs (35,46).

Environmental factors

The hygiene hypothesis (47), indicating reduced microbiologic diversity (48) as a common factor in modern society, is, besides socioeconomy and geography, considered to be the most important environmental factor causing increased incidence of disease. Additionally, possible specific pathogenic bacteria or commensal bacteria combined with abberant immune cells may serve as explanations for the development of disease. Latitude might be an independent risk factor (49) in addition to contamination and pollution causing oxidative stress (50,51).

Smoking is generally accepted as a risk factor in CD and for worsening of disease course by reducing response to treatment, increasing relapse rate, and complications(11), In UC, smoking has a protective effect against the same outcomes of disease (52).

The connection between smoking and disease onset is less clear, but a meta-analysis showed an

OR of 0.58 for UC and 1.76 for CD among smokers (52) in the general population, which could implicate smoking as part of a primary event and not only as a secondary factor influencing the disease course. Passive exposure to smoking during childhood was also shown to influence IBD risk (53). Moreover, a recent investigation suggested that passive smoking was detrimental for the outcome of CD patients (54). A possible relationship between age at diagnosis and smoking was also suggested (55). No single explanation for the mechanism behind smoking and onset of IBD has been postulated; however, among siblings discordant for smoking, smokers tended to develop CD whereas nonsmokers tended to develop UC (56). This finding may suggest an interaction between smoking and genetic susceptibility. In UC, the significantly reduced frequency of perinuclear antineutrophil cytoplasmic antibody (pANCA) positivity among smokers, and a tendency for increased frequency of anti-Saccharomyces cerevisiae antibody (ASCA) positivity, may be supportive of such a mechanism or may be explained by indirect mechanisms, such as a result of disease activity or exposure to treatment (57).

Relationship to microbiology.

Today, the most important cause relationship of IBD, is explained by an imbalance in the microbial host relationship, with mucosal barrier dysfunction and reduced microbial diversity (58). The hygiene hypothesis is an attempt to explain why improvement of hygienic conditions may result in intestinal dysbiosis as a primary event, resulting in IBD among genetically predisposed individuals. The "Cold chain hypothesis" is a more direct explanation, postulating that CD is a result of a defect in the host recognition of pathogenic bacterial components that usually escape the immune response(e.g., Yop molecules), leading to an excessive host response to bacteria, such as Yersinia spp. and Listeria spp., which can survive refrigerator temperature(59,60,61). In support of the hygiene hypothesis are the generally negative associations to the epidemiology of Helicobacter pylori (62) and the inverse association to the prevalence of helminthic colonization (63,64).

It is still an issue if primary pathogens like mycobacterium avium paraturbeculosis (MAP), Jones disease (65) may be an etiologic factor. Problems are related to the biologic methodology. Clinical studies up to now have been inconclusive. A study of seropositivity showed a high

prevalence for IBD, but failed to demonstrate a difference between CD, UC and controls (66).

A meta-analysis of 28 case control studies showed a positive association between MAP and CD, both for enzyme-linked immunosorbent assay (Elisa) and PCR (67), however, a recent examination (68), performed with highly sensitive methods in intestinal mucosa, could not detect the presence of MAP in newly diagnosed, treatment naïve cases, in contrast to many affected cases among hospitalized CD patients on treatment, in the same catchment area. MAP may, therefore be a bystander or elusive at diagnosis appearing during the course of disease, and preferentially in patients on treatment.

Other hospital based studies have demonstrated a geographic covariation related to hospitalization and mortality for IBD and clostridium difficile (69).

Since IBD is most common in the Northern hemisphere, most studies with regard to microbial risk factors have been performed in this region. In addition to improvement in sanitary conditions being responsible for reduced microbial diversity, industrial pollution in society might serve as another explanation for changed environment

Other environmental factors, such as water supply, may act in addition to the instability, primarily caused by the dysbiotic intestine. In a recent study, a strong association between iron concentration in the sources of drinking water and the community incidence of IBD, both CD and UC, was found (51). Other metals showed no association to IBD, opposed to the proposed focus on aluminum as a risk factor . Explanations for the effect of iron might be oxidative stress or

bacterial growth (50,51). Relationship to latitude might also be explained by changes in sun exposure and vitamin D.

Socioeconomic factors.

Several studies have reported on increased incidence of both UC and CD in more densely populated areas (70,71,72,73,74). Both family size and number of older siblings, as well as birth order, have been related to increased risk of UC, and with smaller families and few older siblings related to CD (75), which might be a sign that UC is more directly affected by environmental factors than CD. This explanation was also supported by a shorter interval between first degree

relatives acquiring UC compared to CD (46). The relationships between these diseases and other household related conditions, such as pets, are unclear (76,77,78,79).

It has previously been reported that both UC and CD are affecting white collar more than blue collar employees (80). Further studies among German employees suggested that work in the open air and physical exercise were protective, while being exposed to air conditioned, artificial working conditions or extending and irregular shift working increased the risk of IBD (81). In population based studies in Norway, the incidence of IBD was higher in rural areas with a recent increase in socioeconomic status, based on years of education, compared to urban areas with a stable high socioeconomic level (82,83). The relationship between socioeconomic and sanitary conditions was demonstrated by the fact that availability of a fixed hot water supply in childhood before the age of 11, was associated with CD, formed the basis for the hygiene hypothesis (84).

Nutrition and diet.

Many studies in small cohorts of patients claim that intake of certain diet constituents like fat, refined sugar, fruits, vegetables and fiber affect the expression of IBD. A recent survey of Medline and the Cochrane data base concluded that, based on the current levels of knowledge concerning dietary risk factors for IBD, and the therapeutic efficacy of dietary and nutritional interventions, the results need to be supported by well-designed trials in large cohorts of patients (85). Drug-nutrient interactions, disease location, symptoms, and dietary restrictions can lead to protein energy malnutrition and specific nutritional deficiencies. Nutritional deficiencies are relatively common in IBD, both regarding reduced intake of food, vitamins and minerals. It is estimated that up to 85% of hospitalized IBD patients have protein energy malnutrition, based on abnormal anthropometric and biochemical parameters (86,87). Attention to weight changes, eating habits and GI symptoms are the best guides for the clinician. Any abnormality, regarding general health, clinical or biochemical measurements must be considered as risk factors regarding disease outcome. Specific dietary therapy to avoid symptoms, and supplements to meet nutritional depletion, are active measures to avoid complications to disease. Metabolic dysfunction and

secondary osteoporosis and osteomalacia are serious complications related to malabsorption in CD. A surveillance study in Italy (88), reported that lack of breast feeding was associated with increased risk of both UC (OR 1.5) and CD (OR 1.9). A metanalysis of 14 case-control studies reported on a protective role for breastfeeding in both CD and UC (89). In spite of a French case control study of incident cases with IBD which suggested breast feeding to be a risk factor(90), the preponderance of evidence suggests that breastfeeding is a protective factor for IBD, with a greater effect for CD than UC, based on a recent metanalysis(1).In a recent large prospective study of the role of dietary macronutrients in the etiology of IBD, high total protein intake, specifically animal protein, was associated with a significantly increased risk of IBD (91), in agreement with the previously reported association with consumption of fast

food for both UC (OR 3.4,1.3-3.9) and CD (OR 3.9,1.4-10.6) in a population based incidence

study in Sweden. This study covered retrospectively the 5 years prior to diagnosis of IBD (92).

Total fat and intake of monosaturated and saturated fats have been related to CD, whereas a negative association was found for carbohydrates (93). A relationship to fat consumption was also found for UC, whereas intake of dietary fiber, fruit and vegetables are reported to be protective for both (94,95).

In a study of pre-illness changes in IBD, approximately one third of patients changed their diet

prior to the diagnosis of IBD due to non specific symptoms. Of the patients not changing their diet, moderate and high consumption of margarine (OR = 11.8 and OR = 21.37) was associated with ulcerative colitis, whilst high consumption of red meat (OR = 7.8) and high intake of cheese were associated with Crohn's disease (96).In a retrospective study performed within three years after diagnosis, the results also showed different, but significant associations for both UC and CD with regard to food consumption (93).In Japan the reported increase of CD during the period 1966-1985, was strongly associated to increased intake of animal protein and somewhat less to increased n-6/n-3 polyunsaturated fatty acid ratio (97), by multivariate analysis. A nested case-control study of a prospective cohort study within seven regions in Europe, identified linoleic acid, in contrast to docosahexaenoic acid, as a significant risk factor for the development of UC (98), however, failed to find a significant association between micro- or macronutrients and disease, based on data from partly the same regions (99)It has been speculated that the

reported relationships between changes in food consumption would fit, in a timely manner, with a change of intestinal microbes associated to IBD (100).

Case control studies from Germany (101) and UK (102) demonstrated an association between intake of sugar and CD, another study showed that intake of sugar and smoking were separate but interactive risk factors (103). Associations between both monosaccharide's and disaccharides and CD were also shown in Israel (104), Japan (105) and Italy (106). The general question regarding the carbohydrate hypothesis is, to what extent reporting of increased consumption is related to early change of diet due to onset of disease, or if it represents an etiologic factor. This question may also be raised regarding the increased frequency of bran eaters among patients with CD (107).

Regarding host response to yeast, several studies have shown increased IgG and IgA antibodies to baker's yeast (Saccharomyces cervisiae) in patients with CD but not UC (108,109) as a consequence of intake of wheat. A recent report from studies in twins, however, suggested ASCA to be a marker of shared environment but with a genetic susceptibility, other than NOD2/Card15, as regards the titer level (110).

Recent reports have focused on the possibility of a nutrient-gene interaction, which might be a part of an individualized immunogenic therapy in the future (111).

Mechanisms by way of food consumption might also be further elucidated by studies on the role of epigenetic factors for the development of IBD in the future (112,113).

Micronutrients and microparticles.

Both in food and water supply, metals and minerals as well as other microparticles are abundant, and as such more common as part of pollution in industrialized areas. These particles may act in different ways with the immune system, causing primary or secondary effects. IT has been suggested that exposure to xenobiotic-like metals may induce immune responses in autoimmune diseases. Such reactions have been related to effects of mercury (114), cobalt, zirconium, beryllium, silver and aluminum (115). Especially aluminum is ubiquitous in the Western culture and represents the most widely used trace element in food, water, soil and pharmaceutical agents. Moreover, food additives and processed foods, such as cheese, baked goods, grain products, cake

and pancake mixes, vending machine powdery, milk, cream powder substitute and soy based milk formulae, sugar and frozen dough, add substantial amount to Al intake. Additionally, different substances, when added to water and even water purification procedures, may increase the bioavailability and toxicity in aqueous organisms resulting in facilitating Al entry into the food chain. On these grounds, a hypothesis of a bacterial-metal interaction was put forward as a factor in CD induction (116).

In line with this, the recently reported strong association between iron concentration in the sources of drinking water and the community incidence of IBD, both CD and UC, may support a bacterial-metal interaction. In this study, however, other metals showed no association to IBD, opposed to the proposed focus on aluminum as a risk factor in IBD.

Interactions between microparticles and the immune system, possibly by accumulation in macrophages, has also been postulated as a basis for the use of low microparticle diets in the treatment of IBD (117).

Pathogenesis

With the current state of knowledge IBD pathogenesis seems extremely complex, and extensive studies seek to improve the understanding of relevant mucosal biology. Also Nordic research groups have taken part in this effort, with a series of important studies on gut immunoglobulins, macrophages and different lymphocyte populations in IBD in addition to the immunology of celiac disease (118). Importantly, some of the first publications on calprotectin in the intestinal mucosa came from this translational research environment (119), and subsequent studies (120) also with participation from researchers and clinicians in all Scandinavian countries (121) have established calprotectin as an excellent fecal marker of IBD. Arguably, experimental studies on transgenic mouse models have added significantly to our knowledge of mucosal immunology and these methods are used in scores of research laboratories worldwide. Unlike many others,

Scandinavian IBD research groups tend to work in environments with close contact between laboratory and clinical medicine. Examples of this translational approach are seen in studies on molecular mechanisms in IBD (122,123) also directly aimed at solving clinical problems as e.g. treatment decision making (124).

Disease course

About half of the patients in a population-based study did not require glucocorticosteroids (GCS) during the first year of disease (125) after the initially active disease was treated. Requirement for steroids and 5-aminosalicylic acid was further reduced from the first to the second five years period (126) even before biologics was on the market. Nevertheless, the same study showed a cumulative increased relapse rate, and that repeated individual need for surgery and secondary fistulas were continuous problems during the entire period (11). Importantly, young age at onset is associated with complicated disease and reduced QoL (6).

In UC, extension of disease from proctitis or left-sided colitis to substantial or total colitis was reported over the subsequent years (27). The tendency of relapse in CD seems to continue over at least 10 to 20 years, although reduced disease activity over time and even burnout of disease seems to occur (128). Individual change of diagnosis among CD, UC, and IBD-U has been reported in about 10% of patients during the first year after diagnosis (9,125).

Predictors of disabling CD, at diagnosis, for the subsequent 5 years in a referral center, were age below 40 years, perianal disease, and initial requirement for systemic corticosteroids (129). Stricturing disease and weight loss at diagnosis represented independent risk factors. Patients with CD first diagnosed at acute abdominal surgery showed a lower risk for reintervention and less use of steroids and immunosuppressants during follow-up than those not operated upon at diagnosis (130).

Clinical subtypes

The ability of diagnostic subtyping improved greatly after the introduction of fiber optic endoscopy and histology, mainly related to disease localization and distribution. For CD, the Vienna classification (131), and later also for UC, the Montreal classification (132), are based on endocopic documentation, preceeded by classifications based on global clinical assessments of disease activity (133,134,135,136,137). We are at present in the position of acquiring experience with combined modalities (138,139,140,141). Recent development of wireless videoendoscopy (142,143), and imaging modalities (144), have already been defined as useful for routine use.

Relationships between IBD subtypes and genetics, disease behaviour (37) and functional genomics and protein expression, have shown promising documentation on what we can expect from mucosal (145) and serologic (146) markers in the future.

A relationship to age and gender both for adults (82,83) and children (147) has been discussed for diagnosis, localization and follow up (148). Further, a distinction between primary and secondary as well as localization of fistulas was achieved by the Montreal classification (149,150).

By implementation of genotype, this classification has given important information related to clinical phenotype, such as between ileal and fibrostenotic disease for individuals with NOD2/CARD15 mutations (37), and between these mutations and certain HLA phenotypes or risk of surgery, low weight and younger age at diagnosis and presence of granulomas (151,152). Great variations in frequency of mutation, unrelated to the incidence of Crohn's disease and proportion of ileal location of disease, has been shown in Scandinavia and other Northern European countries. The mutation rate is low in spite of a high incidence rate of IBD (153). In other parts of the world, these mutations are very low or abscent in spite of an increasing incidence of Crohn's disease (154,155,156). Novel candidates, such as DLG5, MDR1, TLR4, ATG16 or gene mutations for Il23/12 are, in spite of associations to disease, still in need of documentation with regard to prognosis or association to clinical subgroups.

By implementation of serologic markers, mainly ASCA and p-ANCA, positivity has been used to separate IBD from non-IBD and Crohn's disease from ulcerative colitis (157,158). ASCA positivity as a prognostic marker has shown a significant relationship to surgery and complicated disease (158). Introduction of new serologic markers with anti-microbial agents, such as anti-OMPC, anti-12 and anti-cBir1, might seem promising (159,160,161,162) for clinical subclassification.

The Montreal classification (132) brought forward controversies, consensus and implications based upon current knowledge of ulcerative colitis. The differentiation between total versus left sided colits in addition to proctitis has given reason for local versus systemic treatment, and to serve as prognostic factor regarding malignancy. More extensive distribution of disease over time, both for initial proctitis and left sided colitis(163) and also, in a subgroup of patients, the regress to less extensive disease, seems evident. In the EC-IBD study over 10 years, most all of

14

the patients with initial proctitis or left sided colitis, had reached the stage of extensive disease by the time of operation (10). In approximately 10% of patients the initial diagnosis may be uncertain, and a change between UC, IBD-U and CD, or between any of them and non-IBD (self limited colitis) during the first years of disease (125) may occur. The good clinical prognosis of extensive disease at diagnosis and the subsequent good prognosis after mucosal healing at one year (164), both probably related to initial intensive treatment, and the relationship to malignancy must all be considered for this subtype (165). Disease behaviour in ulcerative colitis is related to treatment and treatment outcome. The fulminant stage of disease with general systemic involvement of fever, anemia and bowel distension represents a high risk of complications and serious outcomes. This setting is quite different from signs of severe intestinal relapse alone, without systemic affection, which is seen in chronic active inflammation or acute residual disease. In UC, subtypes fall mainly into four cathegories,- primary active with a mild course, primary active with chronic residual disease, chronic active, and increasingly active disease (127,166), based on population based studies.

Genetic susceptibility of UC (39), HLA-DRB susceptibility to pancolitis,surgical resection and etraintestinal manifestations (67),relationship between serologic markers pAnca and UC (68) and significant relation to relapsing disease and 5-ASA, GCS and aza/6MP (57), have been shown.

On the other hand, serologic markers, such as P-ANCA and ASCA, which are strongly related to either UC or CD, have been suggested to be absent in a subgroup of patients with IBDU (157).

Primary sclerosing cholangitis (PSC) shows a strong relationship to IBD, especially UC, which might represent a specific entity of IBD with respect to disease location, disease course, complications as well as predictability after colectomy and liver transplantation. PSC shows an increased tendency of "silent colitis", with a need for less medication than would be expected from patients with extensive disease, increased tendency of rectal sparing, right sided location and backwash ileitis (169). This was reproduced in a recent large study except for backwash ileitis which was only demonstrated in 20% of patients (170). The majority of colectomies are performed due to risk of malignancy. Some PSC patients develop a more aggressive colitis after liver transplantation and the frequency of pouchitis is reported to be higher than among UC patients without PSC (171,172). A shortened survival has been shown in the group with

restorative proctocolectomy (171).

Medical treatment of IBD

The goals of treatment are achievement and maintenance of remission and prevention of flares. The concept of mucosal healing, both in Crohn disease and ulcerative colitis, is becoming increasingly advocated. There are several studies, primarily involving anti-TNF agents (and occasionally immune modifiers); that have shown that the elimination of inflammation (as demonstrated by endoscopic and histologic criteria) results in a decrease in the rate of surgery, the use of corticosteroids, and the rate of hospitalization (164,173,174,175,176,177,178). This supports the use of immune-modifying agents (mercaptopurine or azathioprine) or one of the anti-TNF agents earlier in the course of IBD. In the absence of active inflammation, quiscent disease may appear with IBS-like symptoms needing symptomatic treatment and individual support.

Conventional medical treatment.

Sulphasalazine was the first compound found to be effective in the control of UC (12). After identification of 5-aminosalicylate as the active compound of sulfasalazine, the routine preparations today include Azo-bonded (Sulphalazine, Balsalazine, Olsalazine), slow release (Pentasa), and modified release, pH dependent(Asacol,Salofalk, Mezavant) compounds, for active treatment or during remission, as oral or rectal 5-ASA.

For active disease or a flare of moderate severity, prednisone of 20-40 mg/day is often sufficient, followed by tapering of steroids. Corticosteroids may be administered by various routes

depending on the location and severity of disease; they may be administered intravenously (ie, methylprednisolone, hydrocortisone), orally (ie, prednisone, prednisolone, budesonide, dexamethasone), or topically (ie, enema, suppository, or foam preparations).Corticosteroids are limited by their adverse effects, particularly with prolonged use. Periodic assessment of bone mineral density is recommended for patients taking steroids for more than 3 months. Topical steroids are available for Crohn disease with ileal or ileocecal involvement (179). Despite first-pass metabolism, which limits systemic adverse effects, some absorption occurs over a prolonged period of exposure. Applications for colonic involvement are underway.

Patients are candidates for immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) or anti-TNF agents (infliximab, adalimumab, certolizumab pegol) and or other biologic agents(Cyclosporin A, Tacrolimus) if flares are frequent (>1-2 times) or in fulminant disease, if the duration of steroid use is prolonged (more than a few weeks per year), if reduction of the steroid dose causes recurrence of symptoms (steroid dependent), or if steroids do not appear to be effective (steroid refractory,penetrating disease). Before starting therapy with AZA or 6-MP, patients should undergo assessment of the thiopurine methyltransferase (TPMT) genotype or phenotype. Individuals who have low enzyme activity or are homozygous deficient in the TPMT mutation are at risk of severe leukopenia (sometimes dose dependent), with potential septic complications, and may not be good candidates for therapy with these drugs.

A systemic review of the efficacy of biologic therapies in IBD confirmed that anti-TNF-alpha agents and integrin blockers are effective in inducing remission of active Crohn disease.(186)For Crohn disease, the response rate may be as high as 80%, and the induction of remission rate is 30-50% after a single dose. For ulcerative colitis, the response rates may be as high as 50-70%. For both CD and UC, the clinical remission rates are about 50% of the response rates. Nevertheless, patient reported response rates are generally better than clinical or endoscopic response or remission rates..

Monitoring of biologic treatment includes measurements of trough levels and anti-TNF antibodies (180). Before anti-TNF agents are administered, screening should be done for coexistent infection, including Mycobacterium tuberculosis, and caution is advised if a patient is a carrier for the hepatitis B virus. Biologic compounds for clinical use today include Infliximab, adalimumab, certolizumab, golimumab, natalizumab, vedolizumab as well as generic preparations.

Probiotic agents.

Supplementation of the high-potency probiotic mixtures (181) have been shown in some reports to reduce ulcerative colitis activity in patients with mild to moderate relapsing disease during treatment with 5-ASA. Studies in patients with Crohn disease have been much less promising.

Antibiotics.

Metronidazole and ciprofloxacin are the most commonly used antibiotics in persons with IBD

(182). In UC treatment efficacy is low and partly contraindicated because of an increased risk of developing antibiotic-associated pseudomembranous colitis and increase the risk of Clostridium difficile colitis. In persons with Crohn disease, antibiotics are usedon various indications, most commonly for perianal disease, fistulas, and intra-abdominal inflammatory masses.

Management during Remission.

Medications used to achieve remission should be continued, except steroids, in a lower dose.The duration of treatment should be related to individual risk of relapse, complications and safety aspects, which are all heavily focused in today's research.

Surgical Intervention

Ulcerative colitis is a surgically curable disease. However, Crohn disease can involve any segment of the gastrointestinal tract from the mouth to the anus whereby surgical resection is not curative. Moreover, recurrences are frequent. In addition, repeated need for surgery and bowel resection may result in short gut syndrome and dependence on parenteral nutrition.

Ulcerative colitis.

Surgical intervention (10-30%) is indicated for patients in whom medical therapy fails, for those with colonic dysplasia or malignancy, toxic megacolon and perforation. Up to 30% of patients may require operative management. The surgical options for ulcerative colitis vary (14). Currently, the two most common choices are proctocolectomy with ileostomy and total proctocolectomy with ileoanal anastomosis (IPAA). The major complication of this procedure is postoperative development of acute or chronic pouchitis. IPAA offers an excellent option for younger patients with ulcerative colitis and concerns with body image, but is also associated with a substantial rate of infertility (183). Elective surgery can be performed laparoscopically. For fulminant colitis, the surgical procedure of choice consists of a subtotal colectomy with end ileostomy and creation of a Hartmann pouch.

Crohn disease.

Surgery for Crohn disease (up to 80%) is most commonly performed in cases of complications of the disease (strictures, fistulas). Conservative resection is advocated (including potential

stricturoplasty, as opposed to resective surgery) to preserve bowel length in case additional surgery is needed in the future (184).

Symptomatic enteroenteric fistulas are generally resected, although recurrence is common. Postoperative medical therapy often prevents recurrence, although data are lacking regarding efficacy. A meta-analysis of 9 randomized trials suggested that 5-ASA preparations provide a very modest benefit for maintenance (185). The preferred program of prevention varies between immunomodulators and biologic therapy. The World Gastroenterology Organization (WGO) recommendations for tapering corticosteroids in the peri- and post operative setting depend on the duration of corticosteroid us (186). Before undergoing major elective surgery, women with IBD should stop using combined oral contraception for a minimum of 4 weeks before the surgery.

Diet

In UC, low-residue diet may reduce the frequency of bowel movements. Unlike in UC, diet, such as liquid or predigested formulations may reduce inflammation in CD. Palatability may limit the intake of adequate energy, and parenteral alimentation may be needed.

Multivitamin supplementation is recommended in patients with IBD. The link between vitamin D and IBD may be of particular importance (187,188,189) as low vitamin D levels increase the risk of surgery and hospitalization, both in CD and UC

Steroid users are candidates for vitamin D and calcium supplementation, patients with ileal resections or dysfunction candidates for vitamin B12, and parenteral iron (IM weekly or IV) should be used in patients with chronic iron-deficiency

Reproduction and Pregnancy

Clinicians should review the prescribing information for medications in women who are attempting to conceive, are pregnant, or are breastfeeding (190)All of the aminosalicylates and corticosteroids appear to be safe in women in all phases of fertility, pregnancy, and lactation. Men should avoid sulfasalazine during periods when they and their mates are attempting to become pregnant due to reduced sperm counts. In women with IBD, fertility is normal or only minimally impaired. For immune modifiers, increased birth defects have not been reported, and should be continued throughout the pregnancy Methotrexate (MTX) is contraindicated due to teratogenic effects, and should be discontinued 3 months prior to planned conception.

Most infants born to parents with IBD are healthy. Familial, maternal, and paternal IBD has been linked to preterm birth, which might be explained by genetic mechanisms (191). The prevalence of spontaneous abortion is slightly higher in patients with IBD (12.2%) than in the general population (9.9%). Previous proctocolectomy or ileostomy is not an impediment to successful pregnancy, however, controversy exists regarding the type of delivery (cesarean or vaginal) that is most appropriate when a woman has had ileal pouch/anal anastomosis surgery.Women who have undergone such a procedure should consult with their obstetricians and gastroenterologists. Folate supplements should be taken.

Continuation of TNF-alpha inhibitors during pregnancy is safe (FDA category B), but concerns have been raised about high levels of maternally administered anti-TNF agents being found in the fetal circulation. The manufacturers of infliximab and adalimumab recommend that these 2 agents be discontinued during the third trimester of pregnancy, although there is no documentation of fetal harm. Certolizumab does not cross the placenta.

Both male and female partners receiving methotrexate should use effective contraception for a minimum of 3 months following treatment with this agent. In women who have Crohn disease and small bowel disease and malabsorption, or who have been using antibiotics, oral contraception may have reduced effectiveness (190).

Breastfeeding

Sulfasalazine metabolites can be detected in breast milk. Low concentrations of mesalamine and higher concentrations of its metabolites can also be detected in breast milk, but the significance of this is unknown. In addition, corticosteroids can also be detected in breast milk.

Immune modifiers are excreted in breast milk and should be considered only on a case-by-case basis; either the immune modifier should be discontinued or the infant should be bottle fed.

Antibiotics (metronidazole, ciprofloxacin) should generally be avoided during lactation, because they are excreted in breast milk; either breastfeeding or the drugs should be discontinued. These agents are probably safe for fertility and during pregnancy.

Anti-TNF agents (ie, infliximab, adalimumab) traverse the placenta, whereas certolizumab does not, because of the absence of the Fc fragment. They are found in the cord blood but not in breast milk.

Although small amounts of the topical agents are absorbed and thus may be excreted in breast milk, the concentrations are much lower than those with the oral forms of the same medications. These medications are probably reasonably safe in breastfeeding.

Conclusion

Although significant advances have been made over the last 50 years in the care of patients with IBD, these diseases constitute a huge clinical problem with e.g. approximately 2.2 million affected Europeans. A basic problem is that we still do not know the etiology of the disease processes, and pathogenesis is only partly understood. Thus, there is no causal treatment as of today and an intensive research effort on all aspects of these diseases is still warranted.

Reference list.

1. Mikhailov TA, Furner SE. Breastfeeding and genetic factors in the etiology of IBD in children.World J Gastroenterol.2009;15(3):270-279.

2. Danese S, Sans M, Fiocchi C. IBD: the role of environmental factors.Autoimmun Rev.2004;3(5):394-400.

3. Podolsky DK. Inflammatory Bowel Disease.N Engl J Med.2002;347(6):417-429.

4 .Wolters FL, Russel MG, Sijbrandij J, Ambergen T, Odes S, Riis L et al. Crohn's disease: increased mortality 10 years after diagnosis in a Europeanwide population-based cohort. Gut 2006, 55:510–518.

5. Hoie O, Schouten LJ, Wolters FL, Solberg IC, Riis L, Mougas A et al. Ulcerative colitis: no rise in mortality in a European-wide population-based cohort 10 years after diagnosis. Gut 2007, 56:497–503.

6. Huppertz-Hauss G, Hoivik ML, Langholz E, Odes S, Smastuen M, Stockbrugger R et al. Health related quality of life in inflammatory bowel disease in a European-wide population-based cohort 10 years after diagnosis. Inflamm Bowel Dis 2014 ;21 :337-44.

7. Vernier-Massouille G, Balde M, Salleron J, Turk D, Dupas JL, Mouterde O et al. Natural history of pediatric Crohn's disease: A population based cohort study.Gastroenterology 2008, 135: 1106-13.

8. Moum B, Ekbom A, Vatn MH, Aadland E, Sauar J, Lygren I et al.: Clinical course during the fi rst year after diagnosis in ulcerative colitis and Crohn's disease. Scand J Gastroenterol 1997, 32:1005–1012.

9. Geboes K, Colombel JF, Greenstein A, Jewell D, Sandborn WJ, Vatn MH et al.: Indeterminate colitis: a review of the concept—what is in a name? Infl amm Bowel Dis 2008, 14:850–857.

10. Hoie O, Wolters FL, Riis L, Bernklev T, Aamodt G, Clofent J et al.: Low colectomy rates in ulcerative colitis in an unselected   European cohort followed for 10 years. Gastroenterology 2007, 132:507–515.

11. Solberg IC, Vatn MH, Hoie O, Stray N, Sauar J, Jahnsen J et al.: Clinical course inCrohn's disease: results of a population-based ten-year follow upstudy. Clin Gastroenterol Hepatol 2007, 5:1430–1438.

12. Svarts N, Salazopyrin, a new sulfanilamide preparation. A. Therapeutic results in rheumatic polyarthritis. B. Therapeutic results in ulcerative colitis. C. Toxic manifestations in treatment with sulphanilamide preparations. Acta Med Scand 1942;110:577-98.

13.   Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moyayyedi P et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterology 2011;106:644-59.

14.   Svaninger G, Nordgren S, Oresland T, Hulten L. Incidence and characteristics of pouchitis in the Kock continent ileostomy and the pelvic pouch Scand. J Gastroenterol 1993;28:695- 700.

15. Lazarev WH, Ullman T, Schrayt WH, Kip KE, Saul M, Regueiro M. Small bowel resection in Crohn's disease and the indication for surgery over time: experience from a large tertiary center. Inflamm Bowel Dis 2010; 16:830-5.

16. Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population based study. NEJM 1990;323:1228-33.

17. Ekbom A, Adami HO, Helmick C, Zack M. Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. Lancet 1990; 336:357-59.

18. Eaden JA,Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a metanalysis. Gut 2001;48:526-35.

19. Jess T, Simonsen J, Jorgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. Gastroenterology 2012; 143:375-81.

20. Jorgensen K, Inflammatory bowel disease in primary sclerosing cholangitis:clinical characteristics in liver transplanted and non-transplated patients. Thesis 2013, Faculty of Medicine, University of Oslo, Norway.

21. Shivananda S, Lennard-Jones J, Logan RFA, Fear N, Price A, Carpenter L et al. Incidence of Inflammatory bowel disease across Europe: Is there a difference between north and south? Results of the European collaborative study on inflammatory bowel disease (EC-IBD) Gut 1996; 39: 690-7.

22. Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A et al. Epidemiology of Crohn's disease and ulcerative colitis in a central   Canadian province.Am J Epidemiol.1999;149:916-924.

23. Zheng JJ, Zhu XS, Huang FZ, Gao ZX, Guo ZR, Wang Z et al. Crohn's disease in mainland China: a systematic analysis of 50 years.Chin J Dig. Dis.2005;6:175-181.

24. Desai HG, Gupte PA. Increasing incidence of Crohn's disease in India. Indian JGastroenterol.2005;24:23-24.

25. Logan RFA. IBD incidence: up, down or unchanged? Gut. 1998;42:309-311.

26. Loftus EV. Clinical epidemiology of IBD. Gastroenterology.2004;126 :1504-1517.

27. Baumgart D Eds. Crohn's disease and ulcerative colitis. From Epidemiology and Immunobiology to a Rational Diagnostic and Therapeutic Approach.Springer Verlag, NY   2012.

28. Molodecky NA1, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R,Ghosh S, Barkema HW, Kaplan GG.. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012

Jan;142 :46-54

29. Ng SC, Bernstein CN, Vatn MH, Lakatos PL, LoftusJr EV, Tysk C , on behalf of the Epidemiology and Natural History Task Force of the International Organization of Inflammatory Bowel Disease (IOIBD). Geographical variability and environmental risk factors in inflammatory bowel disease. Gut 2013; 62: 630-49.

30. Wolters F, Russel MG, Sijbrandij J, Ambergen T, Odes S, Riis L et al.: Phenotype atdiagnosis predicts recurrence rates in Crohn's disease. Gut 2006, 55:1124–1130.

31. Bernstein CN, Wajda A, Svenson LW, Mackenzie A, Jackson M, Fedorak R et al.: The epidemiologyof infl ammatory bowel disease in Canada: a population-based study. Am J Gastroenterol 2006,101:1559–1568.

32. Glick SR, Carvalho RS. Inflammatory bowel disease. Pediatrics in review 2011; 32: 14-25.

33. Halfvarson J, Bodin L, Tysk C, Lindeberg E, Jãrnerot G. Inflammatory bowel disease in a Swedish twin cohort. A long term follow up of concordance and clinical characteristics. Gastroenterology 2003, 24:1767- 73.

34. Satsangi J, Grootsholten L, Holt H, Jewell D. Clinical patterns of familial inflammatory bowel disease. Gut 1996, 38:738-41.

35. Bengtson M-B, Solberg IC,Aamodt G, Jahnsen J, Moum B, Sauar J et al. Clustering in time of familial IBD separates ulcerative colitis from Crohn's disease. Inflamm Bowel Dis 2009, 15: 1867-74.

36. Slatkin M. Epigenetic inheritance and the missing inheritability problem. Genetics 2009; 182:845-50..

37. Abreu MT, Taylor KD, Lin YC, Hang T, Galannie J, Landers CJ et al. Mutations in NOD 2 are associated with fibrostenotic disease in patients with Crohn's disease. Gastroenterology 2002, 123:679-88.

38. Strober W, Fuss I, Mannon P. The fundamental basis of inflammatory bowel disease. J Clin Invest 2007, 117: 514-21.

39. Franke A, Belchun T, Karlsen TH, Sventoraityte J, Nikolaus S, Mayr G et al. Sequence variants in IL10, ARPC2 and multiple other loci contribute to ulcerative colitis susceptibility. Nat Genet 2009, 41: 1319-23.

40. Orholm M, Binder V, Sorensen TI, Rasmussen LP, Kyvik KD. Concordance of inflammatory bowel disease   among Danish twins. Results of a nationwide study. Scand J Gastroenterol 2000;35(10):1075-81.

41. Helio T, Halme L, Lappalainen M, Fodstad H, Paavola-Sakki P, Turinen U et al. Card15/NOD2 gene variants are associated with familially occurring and complicated forms of Crohn's disease. Gut 2003, 52:558-562.

42. Bengtson M-B, Solberg IC, Aamodt G, Sauar J, Jahnsen J, Moum B et al. Familial aggregation in Crohn's disease and   ulcerative colitis in a Norwegian population- based cohort followed for ten years. Journal of Crohn's and Colitis 2009, 3: 92-99.

43. Bayless TM, Tokayer AZ, Polito JM 2nd, Quaskey SA, Melitis ED, Harris ML et al. Crohn's disease concordance for site and clinical type in affected family members – potential heredity influence. Gastroenterology 1996; 111:573-9.

44. Polito JM 2nd, Childs B, Melitis ED, Tokayer AZ, Harris ML, Bayless TM et al. Crohn's disease: influence of age at diagnosis on site and clinical type of disease. Gastroenterology 1996;111:580-6.

45. Polito JM2nd, Rees RC, Childs B, Mendeloff A, Harris ML, Bayless TM et al. Preliminary evidence for genetic anticipation in Crohn's disease. Lancet 1996;347:798-800.

46. Binder V, Orholm M. Familial occurrence and inheritance studies in inflammatory bowel disease. Neth J Med 1996;48:53-56.

47. Guarner F, Bourdet-Sicard R, Brandtzaeg P, gill SH, McGuir R, van Eden W et al. Mechanismsof disease: the hygiene hypothesis revisited. Nat Clin Pract Gastroenterol Hepatol 2006, 3:275–284.

48. Ley R, Peterson D, Gordon J: Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell 2006, 124:837–848.

49. Hildebrand H. On the generality of the latitudinal diversity gradient. Am Nat 2004, 163:192-211.

50. Rezaie A, Parker RD, Abdollahi M. Oxidative stress and pathogenesis of inflammatory bowel disease: an epiphenomenon or the cause? Dig Dis Sci 2007; 52: 2015-21.

51. Aamodt G, Bukholm G, Jahnsen J, Moum B, Vatn MH. The association between water supply and infl ammatory bowel diseasebased on a 1990–1993 cohort study in southeastern

Norway. Am J Gastroenterol 2008, 168:1065–1072.

52. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandin RS. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc 2006, 81:1462–1471.

53. Russel RK, Farhodi R, Wilson M, Drummond H, Satsangi J, Wilson DC. Perinatal passivesmoke exposure may be more important than childhoodexposure in the risk of developing childhood IBD. Gut 2005, 54:1500–1501.

54. van der Heide F, Dijkstra A, Weersma RK, Albersnagel FA, van der Logt EM, Faber KN. Effects ofactive and passive smoking on the disease course of Crohn'sdisease and ulcerative colitis. Infl ammatory Bowel Dis 2009, 15:1199–1207.

55. Regueiro M, Kip EK, chenugo O, Hagazi RA, Plevy S. Cigarette smokingand age at diagnosis of infl ammatory bowel disease.Infl amm Bowel Dis 2005, 11:42–47.

56. Bridger S, Lee JCW, Bjarnason I, Jones JE, Macpharson AJ. Inf ammatorybowel disease. In siblings with similar genetic susceptibilityfor infl ammatory bowel disease, smokers tend to developCrohn's disease and non-smokers develop ulcerative colitis. Gut 2002, 51:21–25.

57. Hoie O, Aamodt G, Vermeire S, Bernklev T, Odes S, Wolters FL et al.: Serological markersmay predict disease course in ulcerative colitis. Astudy in an unselected population-based cohort followed for 10 years. J Crohn's Colitis (JCC) 2008, 2:114–122.

58. Frank DNA, St Amand AL, Feldman RA, Boedeker EC, Harpez N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Nat Acad Sci 2007; 104: 13780-85.

59. Hugot J-P, Alberti C, Berrebi D, Bingen E, Cezard J-P. Crohn's disease: the cold chain hypothesis. Lancet 2003; 362: 2012-15.

60. Forbes A, Kalantzis T. Crohn's disease: the cold chain hypothesis. Int J Colorectal Dis 2006; 21: 399-401.

61. Malekzadeh F, Alberti C, Nouraei M, Vahedi H, Zaccaria I, Meinzer U et al. Crohn's disease and early exposure to domestic refrigeration. Plos One 2009;4(1):e4288, epub ahead   of print.

62. Luther J, Dave M, Higgins PDR, Kao JY. Association between Helicobacter pylori infection and inflammatory bowel disease: a meta-analysis and systematic review of the literature. Inflamm Bowel Dis. 2009;16:1077-84.

63. Koloski N-A, Bret L, Radford-Smith G. Hygiene hypothesis in inflammatory bowel disease: a critical review of the literature. World J Gastroenterol. 2008;14:165–173.

64. Korzenik JR. Past and current theories of etiology of IBD: toothpaste,   worms, and refrigerators. J Clin Gastroenterol. 2005;39, 4 suppl 2:S59–65.

65. Chacon O, Bermudez LE, Barletta RG. Johne's disease, inflammatory bowel disease, and Mycobacterium paratuberculosis. Annu Rev Microbiol.2004;58:329–363.

66. Bernstein CN, Blanchard JF, Rawsthorne P, Collins MT. Population-based case control study of seroprevalence of Mycobacterium paratuberculosis in patients with Crohn's disease and ulcerative colitis. J Clin Microbiol. 2004;42:1129–1135.

67. Feller M, Huwiler K, Stephan R, alpeter E, Shang A, furrer H et al. Mycobacterium avium subspecies paratuberculosis and Crohn's disease: a systematic review and meta-analysis [see comment] Lancet Infect Dis. 2007;7:607–613.

68. Ricanek P, Lothe SM, Szpinda I, Jorde AT, Brackmann S, Perminow G et al. Paucity of mycobacteria in mucosal bowel biopsies from adults and children with early inflammatory bowel disease. Journ Crohn's Colitis 2010; 4:561-66.

69. Sonnenberg A. Similar geographic variations of mortality and hospitalization associated with IBD and Clostridium difficile colitis. Inflamm Bowel Dis 2010;16:487-93.

70. Ekbom A, Adami HO, Helmick CG, Jonzon A, Zack MM. Perinatal risk factors for inflammatory bowel disease: a case-control study. Am J Epidemiol. 1990;132:1111–1119.

71. Klement E, Lysy J, Hoshen M, Avitan M, Goldin E, Israeli E. Childhood hygiene is associated with the risk for inflammatory bowel disease: a population-based study. Am J Gastroenterol. 2008;103:1775–1782.

72. Radon K. Contact with farm animals in early life and juvenile inflammatory bowel disease: A case-control study. Pediatrics. 2007;120:354–361.

73. Wurzelmann JI, Lyles CM, Sandler RS. Childhood infections and the risk of inflammatory bowel disease. Dig Dis Sci. 1994;39:555–560.

74. Green C, Elliott L, Beaudoin C, Bernstein CN. A population-based ecologic study of inflammatory bowel disease: searching for etiologic clues. Am J Epidemiol. 2006;164:615–623. discussion 624-628.

75. Montgomery SM, Lambe M, Wakefield AJ, Pounder RE, Ekbom A. Siblings and the risk of inflammatory bowel disease. Scand J Gastroenterol. 2002;37: 1301–1308.

76. Lashner BA, Loftus EV., Jr. True or false? The hygiene hypothesis for Crohn's disease. Am J Gastroenterol. 2006;101:1003–1004.

77. Amre DK, Lambrette P, Law L, et al. Investigating the hygiene hypothesis as a risk factor in pediatric onset Crohn's disease: a case-control study. Am J Gastroenterol. 2006;101:1005–1011.

78. Bernstein CN, Rawsthorne P, Cheang M, Blanchard JF. A population-based case control study of potential risk factors for IBD Am J Gastroenterol. 2006;101:993–1002.

79. Feeney MA, Murphy F, Clegg AJ, Trebble TM, Sharer NM, Snook JA. A case-control study of childhood environmental risk factors for the development of inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2002;14:529–534.

80. Sonnenberg A. Disability from inflammatory bowel disease among employees in West Germany. Gut 1989;30:367-70.

81. Sonnenberg A. Occupational distribution of inflammatory bowel disease among German employees. Gut 1990;31:1037-40.

82. Moum B, Vatn MH, Ekbom A, Aadland E, Fausa O, Lygren I et al. Incidence of ulcerative colitis and indeterminate colitis in four counties of south-eastern Norway 1990-1993. A large prospective population-based study. Scand J Gastroenterol 1996;31:356-60.

83. Moum B, Vatn MH, Ekbom A, Aadland E, Fausa O, Lygren I et al. Incidence of Crohn's disease in four counties of south-eastern Norway 1990-1993. A large prospective population-based study. Scand J Gastroenterol 1996;31:350-54.

84. Duggan AE, Usmani I, Neal KR, Logan RF. Appendicectomy, childhood hygiene, Helicobacter pylori status, and risk of inflammatory bowel disease: a case control study. Gut 1998;43:494-8.

85. Yamamoto T, Nakahigashi M, Saniabadi AR. Review article: diet and inflammatory bowel disease--epidemiology and treatment. Aliment Pharmacol Ther 2009; 30:99-112.

86. Graham TO, Kandil HM. Nutritional factors in inflammatory bowel disease. Gastroenterol Clin N Am, 2002;31:203-218.

87. Han PD, Burke A, Baldassano N, Rombeau JL, Lichtensein GR. Nutrition   and

inflammatory bowel disease. Gastroenerol Clin N Am 1999;28: 423-43.

88. Corrao C, A Traguone, R Caprilli, Trallori G, Papi C, Andreoli A et al. Risk of inflammatory bowel disease attributable to smoking, oral contraception and breast feeding in Italy: a nationwide case-control study. Int.J.Epidemiol 1998;27:397-404.

89. Klement E, Cohen RV, Boxman J, Joseph A, Reif S. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis Am J Clin Nutr. 2004;80:1342–1352.

90. Baron S, Turck D, Leplat C et al. Environmental risk factors in paediatric inflammatory bowel diseases: a population based case control study. Gut 2005;54:357-363.

91. Jantshou P, Morois S, Clavel-Chapelon F, Boutron-Ruault MC, Carbonell F. Animal protein intake and risk of inflammatory bowel disease: The E3N prospective study. Am J Gastroenterol 2010; 105: 2195-201.

92. Persson P-G, Ahlbom A, Hellers G.Diet and Inflammatory Bosel Disease: A Case-Control Study. Epidemiology 1992;3:47-52.

93. Amre DK, D'Souza S, Morgan K, Seidman G, Lambrette P, Grimard G et al. Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children. Am J Gastroenterol. 2007;102:2016–2025.

94. Geerling BJ, Dagnelie PC, Badart-Smook A, Russel MG, Stockbrugger RW, Brummer RJ. Diet as a risk factor for the development of ulcerative colitis. Am J Gastroenterol. 2000;95:1008–1013.

95. Sakamoto N, Kono S, Wakai K, fukuda Y, Satomi M, Shimoyama T et al. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. Inflamm Bowel Dis. 2005;11:154–163.

96. Maconi G, Ardizzone S, Cucino C, Bezzio C, Russo AG, Bianchi-Porro G. Pre-illness changes in dietary habits and diet as a risk factor for inflammatory bowel disease: a case-control study. World J Gastroenterol. 2010; 16: 4297- 304.

97. Shoda R, Matsueda K, Yamato S, Uemada N. Epidemiologic analysis of Crohn's disease in Japan: increased dietary intake of n-6 polyunsaturated fatty acids and animal protein relates to the increased incidence of Crohn's disease in Japan. Am J Clin Nutr 1996;63:741-45.

98. Hart AR et al. Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and Aetiology of ulcerative colitis: a nested case-control study within a European prospective cohort study. Gut

2009;58:1606-11.

99. Hart AR, Luben R, Olsen A et al. Diet in the aetiologyof Ulcerative Colitis: A European Prospective Cohort Study. Digestion 2008;77:57-64.

100. Azakura H, Suzuki K, Kitahora T, Morizane T. Is there a link between food and intestinal microbes and the occurrence of Crohn's disease and ulcerative colitis? J Gastroenterol Hepatol 2008;23:1794-801.

101. Martini GA, Brandes JW. Increased consumption of refined carbohydrates in Patients with Crohn's disease. Klin.Wschr.1976;54:367-71.

102. Penny WJ, Mayberry JF, Aggett Pjet al. Relationship between trace elements, sugar consumption, and taste in Crohn's disease. Gut 1983;24:288-92.

103. Katschinski B, Logan RFA, Edmond M, Langman MJS. Smoking and sugar intake are separate but interactive risk factors in Crohn's disease. Gut 1988; 29:1202-06.

104. Silkoff K, Hallak A, Yegena L, Rozen P, Meyberry J, Rhodes JF et al. Consumption of refined carbohydrate by patients with Crohn's disease in Tel-Aviv-Yafo. Postgrad Med J 1980;56:842-46.

105. Matsui T, Iida M, Fujishima M, Imai K, Tsuneyoshi Y. Increased sugar consumption in Japanese patients with Crohn's disease. Gastroenterol Jpn 1990;25:271.

106. Tragnone A, Valpiani D, Miglio F, Elmi G, Bazzocchi G, Pipitone E et al. Dietary habits as risk factors for inflammatory bowel disease. Eur J Gastroenterol Hepatol 1995;7:47-51.

107. James AH. Breakfast and Crohn's disease. Brit Med J 1977;1:943-45.

108. Young CA, Sonnenberg A, Burns EA. Lymphocyte proliferation response   to Baker's yeast in Crohn's disease. Digestion 1994;55:40-43.

109. Mckenzie H, Main J, Pennington CR, Parrat D. antibody to selected strains of Saccharomyces cervisiae(baker's and brewer's yeast) and candida albicans in Crohn's disease. Gut 1990;31:536-38.

110. Halfvarson J, Standaert-Vitse A, Järnerot G et al. Anti-saccharromyces cervisiae antibodies in twins with inflammatory bowel disease. Gut 2005;54:1237-43.

111. Lee G, Buchman AL. DNA-driven nutritional therapy of inflammatory bowel disease.

Nutrition 2009; 25; 885-91

112. Beaudet AL. Epigenetics and complex human disease: is there a role in IBD? J Pediatr Gastroenterol Nutr 2008; 46 suppl 1:E2.

113. Lin Z, Hegarty JP, Cappel J, Yu W, Chen X, Faber P, Wang Y, Kelly A, Poritz L, Peterson B, Schreiber S, Fa JB, Koltun W. Identification of disease-associated DNA methylation in intestinal tissues from patients with inflammatory bowel disease. Clin Genet 2010; Sep 16. doi: 10.1111/ j.1399-0004.2010.01546.x. [Epub ahead of print].

114. Kosuda LL, Greiner DL, Bigazzi PE.Mercury-induced renal autoimmunity Changes in RT6+ T-lymphocytes of susceptible and resistant rats. Environ Health Perspect 1993;101:178-85.

115. Aaron Lerner. Aluminum is a potential environmental factor for Crohn's Disease induction. Extended hypothesis. Annals of the New York Academy of Sciences 2007; 1107: 329-45.

116. Perl DP, Fogarty U, Harpaz N, Sachar D. Bacterial-metal interactions: the potential role of aluminum and other trace elements in the etiology of Crohn's disease. Inflamm Bowel Dis 2004;10:881-83. 123.

117. Lomer MCE, Harvey RSJ, Evans SM, Thompson RPH, Powell JJ. Efficacy and tolerability of a   low mictoparticle diet in a doubble blind, randomized, pilot study in   Crohn's disease. Eur J Gastroenterol Hepatol 2001; 13: 101-06.

118. Brandtzaeg P, Carlsen HS, Halstensen TS. The B-cell system in inflammatory bowel disease. Adv Exp Med Biol. 2006;579:149-67.

19. Bjerke K, Halstensen TS, Jahnsen F, Pulford K, Brandtzaeg P. Distribution of macrophages and granulocytes expressing L1 protein (calprotectin) in human Peyer's patches compared with normal ileal lamina propria and mesenteric lymph nodes. Gut. 1993;34:1357-63.

120. Røseth AG, Fagerhol MK, Aadland E, Schjønsby H. Assessment of the neutrophildominating protein calprotectin in feces. A methodologic study. Scand J Gastroenterol. 1992;27:793-8.

121. Sipponen T, Björkesten CG, Färkkilä M, Nuutinen H, Savilahti E, Kolho KL. Faecal calprotectin and lactoferrin are reliable surrogate markers of endoscopic response during Crohn's disease treatment. Scand J Gastroenterol. 2010;45:325-31.

122. Coskun M, Bjerrum JT, Seidelin JB, Troelsen JT, Olsen J, Nielsen OH. miR-20b,   miR-98, miR-125b-1*, and let-7e* as new potential diagnostic biomarkers in ulcerative colitis. World J

Gastroenterol. 2013;19:4289-99. doi: 10.3748/wjg.v19.i27.4289.

123. Granlund Av, Flatberg A, Østvik AE, Drozdov I, Gustafsson BI, Kidd M, Beisvag V, Torp SH, Waldum HL, Martinsen TC, Damås JK, Espevik T, Sandvik AK. Whole genome gene expression meta-analysis of inflammatory bowel disease colon mucosa demonstrates lack of major differences between Crohn's disease and ulcerative colitis. PLoS One. 2013;8:e56818.

124. Olsen T, Goll R, Cui G, Christiansen I, Florholmen J. TNF-alpha gene expression in colorectal mucosa as a predictor of remission after induction therapy with infliximab in ulcerative colitis. Cytokine 2009;46:222-7.

125. Henriksen M, Jahnsen J, Lygren I, Sauar J, Schulz T, Stray N et al.: Change of diagnosis during the fi rst years after   onset of inflammatory bowel disease: results of a prospective follow up study (the IBSEN study). Scand J Gastroenterol 2006, 41:1037–1043.

126. Solberg IC, Lygren I, Jahnsen J, Aadland E, Hoie O, Cvancarova M et al.: Clinical course during the fi rst teten years of   ulcerative colitis: results from a population-based inception cohort (IBSEN Study).   Scand J Gastroenterol 2009, 44:431–440.

127. Langholz E, Munkholm P, Davidsen M, Binder V. Course of ulcerative colitis: analysis of change in disease activity over years. Gastroenterology 1994, 107:3–11.

128. Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort   of Crohn's disease patients. Scand J Gastroenterol 1995, 30:699–707.

129. Beaugerie L, Seksik P, Nion-Larmurier I: Predictors of Crohn's disease. Gastroenterology 2006, 130:650–656.

130. Loly C, Belaiche J, Louis E: Predictors of severe Crohn's disease. Scand J Gastroenterol. 2008, 43:948–954.

131. Gasche C, Scholmerich J, Brynskov J, D'Haens G, Hanauer SB, Irvine J et al. A simple classification of Crohn's disease: Report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998.   Inflamm Bowel Dis. 2000, 6: 8-15.

132. Silverberg MS, Satsangi J, Ahmad T, Arnott IDR, Bernstein CN, Brant SR et al. Toward an intergrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working partyof the 2005 Montreal congress of Gastroenterology. Can J Gastroenterol 2005,19 suppl A: 5A- 36A.

133. Lennard-Jones JE. Classification of inflammatory bowel disease. Scand J Gastroenterol

1989, 24 suppl 170: 16-9.

134. Rachmilewitz D. Coated mesalazine(5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. Br Med J 1989, 298: 82-6.

135. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid for mildly to moderately active ulcerative colitis. N Eng J Med 1987, 317: 1625-29.

136. Walmsley RS, Ayres RC, Pounder RS, Allan RN. A simple clinical colitis activity index. Gut 1998, 43: 29-32.

137. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955, ii:1045-48.

138. D'Haens G, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine et al. A review of activity indices and efficacy points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology 2007, 132: 763-86.

139. IBD Working Group of the European society for pediatric gastroenterology, hepatology and nutrition. Inflammatory bowel disease in children and adolescents: recommendations for diagnosis- the Porto criteria. J Pediatr Gastroenterol Nutr 2005, 41: 1-7.

140. Tibble JA, Bjarnason I. Fecal calprotectin as an index of intestinal inflammation. Drugs Today 2001, 37: 85-96.

141. Henriksen M, Jahnsen J, Lygren I, Stray N, Sauar J, Vatn MH et al. C-reactive protein: A predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population based study. Gut 2008, 57: 1518-23.

142. Mazzarolo S, Brady P. Small bowel capsule endoscopy: A systematic review. South Med J 2007, 100:274-80.

143. Thomson M, Fritscher-Ravens A, Mylonaki M, Swain P, Eltumi M, Heuschkel R et al. Wireless capsule endoscopy in children: A study to assess diagnostic yield in small bowel disease in pediatric patients. J Pediatr Gastroenterol Nutr 2007, 44:192-7.

144. Scotiniotis I, Rubesin SE, Ginsberg GG. Imaging modalities in inflammatory bowel disease. Gastroenterol Clin iorth Am 1999, 28: 391-421.

145. Bevins CL, Stange EF, Wehkamp J. Decreased Paneth cell defensin expression in ileal Crohn's disease is independent of inflammation, but linked to the NOD2 1007fs genotype. Gut

2009, 58:882-3.

146.   Papp M, Norman GL, Altorjay I, Lakatos PL. Utility of serological markers in inflammatory bowel disease: gadget or magic? World J Gastroenterol 2007, 13:2028-36.

147.   Perminow G, Brackmann S, Lyckander LG, Franke A, Borthne A, Rydning A et al. A characterization in childhood inflammatory bowel disease, a new population-based inception cohort from south-eastern Norway, 2005-2007, showing increased incidence in Crohn's disease. Scand J Gastroenterol 2009; 44:446-56.

148.   Olbjorn C, Nakstad B, Smastuen MC, Thiis-Evensen E, Vatn MH, Perminow G. Earlyanti-TNF treatment in pediatric Crohn's disease. Predictors of clinical outcome in a population-based cohort of newly diagnosed patients.Scand J Gastroenterol 2014; 49.1425-31.

149.   Louis E, Collard A, Oger AF et al. Behaviour of Crohn's disease according to the Vienna classification : changing pattern over the course of the disease. Gut 2001, 49: 777-82.

150.   Levy C, Tremaine WJ. Management of internal fistulas in Crohn's disease. Inflamm Bowel Dis 2002, 8:106-11.

151.   Ahmad T, Marshall SE, Jewell D. Genetics of inflammatory bowel disease: The role of the HLA complex. World J Gastroenterol 2006, 12: 3628-35.

152. Van Limbergen J, Russel RK, Nimmo ER, Satsangi J. The genetics of inflammatory bowel disease. Am J Gastroenterol 2007, 102:2820-31.

153. Hampe J, Grebe J, Nicolaus S, Solberg IC, Croucher PJ, Mascheretti S et al.The NOD2 genotype and clinical course of Crohn's disease. Lancet 2002;359:1661-65.

154. Qui-Sha G, Bing X, Yui J, Yan QJL. NOD2 3020 InsC frame shift mutation is not associated With inflammatory bowel disease in Chinese patients of HAN nationality. World J Gastroenterol 2004, 10:1069-71.

155. Inoue N, Tamura K, Kinouchi Y, Fukuda Y, Takanahashi S, Ogura Y et al. Lack of common NOD2 variants in Japanese patients with Crohn's disease. Gastroenterology 2002, 123:86-91.

156. Jyual G, Amre D, Midha V, Sood A, Seidman E, Thelma BK. Evidence of allelic heterogeneity for associations betweenthe NOD2/Card15 gene and ulcerative colitis among north Indians. Alimentary Pharmacollogy and therapeutics 2007, 26:1325-32.

157. Joossens S, Reinisch W, Vermeire S, Sendid B, Poulain D, Peeters M. The value of

serologic markers in indeterminate colitis : a prospective follow-up study. Gastroenterology 2002,122, 1242-1247.

158. Solberg IC, Lygren I, Cvankarova M, Jahnsen J, Stray N, Sauar J et al. Predictive value of serologic markers in a population based Norwegian cohort with inflammatory bowel disease. Inflamm Bowel Dis 2009, 15: 406-14.

159. Targan SR, Landers CJ, Yang H, Lodes MJ, Chang Y, Papedakis KA et al. Antibodies to CBir1 flagellin define a unique   response that is associated independently to complicated Crohn's disease. Gastroenterology 2005,128:2020-28.

160. Mow WS, Vasiliauskas EA, Lin YC, Fleschner PR, Papedakis KA, Taylor KD et al. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. Gastroenterology 2004, 126: 414-24.

161.   Arnott ID, Landers CJ, Nimmo EJ, Drummond HE, Smith BK, Targan SR et al. Sero-reactivity to microbial components in Crohn's disease is associated with disease severity and progression but not NOD2/Card15 phenotype. Am J Gastroenterol 2004, 99: 2376-84.

162. Dotan I. Serologic markers in inflammatory bowel disease: tools for better diagnosis and disease stratification. Expert Rev Gastroenterol hepatol 2007, 1:65-74.

163. Moum B, Ekbom A,Vatn MH, Aadland E, Sauar J, Lygren I et al. Inflammatory bowel disease: re-evaluation of the diagnosis in a prospective population basedstudy in southeastern Norway. Gut1997, 40: 328-32.

164. Froeslie KF, Jahnsen J, Moum BA, Vatn MH and the IBSEN study group. Mucosal healing in inflammatory bowel disease: Results from a Norwegian population-based cohort. Gastroenterology 2007,133:412-22.

165. Brackmann S, Andersen SN, Aamodt G, Langmark F, Clausen OPF, Aadland E et al. Relationship between clinical parameters and the colitis-colorectal cancer interval in a cohort of patients with colorectal cancer in inflammatory bowel disease. Scand J Gastroenterol 2009, 44: 46-55.

166. Hoie O, Wolters F, Riis L, Aamodt G, Solberg IC, Bernkles T et al. Ulcerative colitis: patients characteristics may predict 10-years disease recurrence in a European-wide population based cohort. Am J Gastroenterol 2007, 102: 1692-1701.

167. Annese V, Piepoli A, Latiano A, Lombardi G, Napolitano G, Caruso N et al. HLA-DRB1 alleles may influence disease   phenotype in patients with inflammatory bowel disease: A

critical reappraisal with review of the literature. Dis Colon Rectum 2005; 48:57-65.

168. Frenzer A, Fierz W, Rundler E, Hammer B, Binek J. Atypical cytoplasmic and perinuclear anti-cytoplasmic antibodies in patients with inflammatory bowel disease. J Gastroenterol Hepatol 1998, 13: 950-54.

169. Lofthus EV, Harewood GC, Lofthus CG, Tremaine WJ, Harmsen WS, Zinsmeister AR et al. Inflammatory Bowel Disease. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. Gut 2005, 54: 91-96.

170.   Jorgensen KK, Scryb C, Lundin K, Clausen OPF, Aamodt G, Schrumpf E et al. Clinical characterization in liver transplanted and nontransplated patients with primary sclerosing cholangitis. Inflamm bowel dis 2012; 18: 536-45.

171. Gorgun E, Remzi FH, Manillich E, Preen M, Shen B, Fazio VW. Surgical outcome in patients with primary sclerosing cholangitis undergoing ileal pouch-anal anastomosis: a case-control study. Surgery 2005, 138: 631-7.

172. Grucela AL, Steinhagen RM. Restorative proctocolectomy and ileal pouch-anal anastomosis for ulcerative colitis after liver transplantation for primary sclerosing cholangitis: case report and review of literature. Am Surg 2005, 71: 362-5.

173. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis. Sep 2009;15:1295-301.

174. Baert F, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease.Gastroenterology 2010;138:463-8.

175. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl Med.   2010; 362:1383-95.

176.   Ha C, Kornbluth A. Mucosal healing in inflammatory bowel disease: where do we stand?. Curr Gastroenterol Rep. Dec 2010;12:471-8.

177. Feagan BG, Lémann M, Befrits R, Connell W, D'Haens G, Ghosh S, et al. Recommendations for the treatment of Crohn's disease with tumor necrosis factor   antagonists: an expert consensus report. Inflamm Bowel Dis 2012;18:152-60.

178. Hanauer SB. Crohn's disease: step up or top down therapy. Best Pract Res Clin Gastroenterol. 2003;17:131-7.

179. Thomsen OO, Cortot A, Jewell D, Phil D, Wright JP, Winter T et al. for the International Budesonide-Mesalamine group. A comparison of Budesonide and Mesalamine for active Crohn's disease. NEJM 2001; 339: 370-74.

180. Bendtzen K, Ainsworth M, Steenholdt C, Thomsen OO, Brynskov J. Individual medicine in inflammatory bowel disease: Monitoring bioavailability, pharmacokinetics and immunogenecity of anti-tumour necrosis factor-alpha antibodies. Scand J Gastroenterol 2009;44:774-81.

181. Hedin C, Whelan K, Lindsay JO. Evidence for the use of probiotics and prebiotics in inflammatory bowel disease: a review of clinical trials. Proc Nutr Soc. 2007;66:307- 15.

182. Khan KJ, Ullman TA, Ford AC, Abreu MT, Abadir A, Marshall JK et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 2011;106:661-73.

183. Oresland T, Palmblad S, Ellstrom M, Berndtsson I, Crona N, Hulten L. Gynecological and sexual function relate to anatomical changes in the female pelvis after restorative proctocolectomy. Int. J. col.dis. 1994;9:77-81.

184. Ramirez RL, Fleshner P. Reoperative Inflammatory Bowel disease Surgery. Clin Colon Rectal Surg 2006; 19:195-206.

185. Gordon M, Naidoo K, Thomas AG, Akobeng AK. Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database Syst ev. 2011;(1):CD008414.

186. World Gastroenterology Organisation (WGO). World Gastroenterology Organisation Global Guideline. Inflammatory bowel disease: a global perspective. Munich, Germany: World Gastroenterology Organisation (WGO); 2009.

187. Helwick C. Low vitamin D exacerbates inflammatory bowel disease. Medscape Medical news [serial online]. May 21, 2013; Accessed May 27, 2013. Available at http://www.medscape.com/viewarticle/804509.

188. Ananthakrishnan AN, Cagan A, Gainer VS, Cai T, Cheng SC, Savova G et al. Normalization of vitamin D status is   associated with reduced risk of surgery in Crohn's diseaseand hospitalization in inflammatory bowel disease: a   prospective study. Inflamm bowel dis 2013; 19: 1921-27.

189. Ardizzone S, Cassinotti A, Bevilacqua M, Clerici M, Porro GB. Vitamin D and inflammatory bowel disease. Vitam horm 2011; 86: 367-77.

190. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. Sexual and reproductive health for individuals with inflammatory bowel disease. London (UK): Faculty of Sexual and Reproductive Healthcare (FSRH); 2009.

191. Bengtson MB, solberg IC, Aamodt G, Jahnsen J, Moum B, Vatn MH, IBSEN study group. Relationship between inflammatory bowel disease and perinatal factors: both maternal and paternal disease are related to preterm birth of offspring. Inflamm bowel dis 2010;16: 847-55.