Natural History and Complications of IBD

Morten H. Vatn, MD

Corresponding author
Morten H. Vatn, MD
The Institute of Clinical Epidemiology and Molecular Biology (EpiGen), Faculty Division AHUS, University of Oslo, Medical Clinic, Oslo University Hospital, Rikshospitalet, 0027 Oslo, Norway.
E-mail: m.h.vatn@medisin.uio.no

Current Gastroenterology Reports 2009, **11:**481–487
Current Medicine Group LLC ISSN 1522-8037
Copyright © 2009 by Current Medicine Group LLC

Inflammatory bowel diseases (IBD), mainly ulcerative colitis and Crohn's disease, are chronic, heterogenic, lifelong illnesses with young age of onset and a great potential for disability. The natural history of these diseases is influenced by multiple factors of environmental and genetic origin. Multidisciplinary research has increased our knowledge of the mechanisms involved during the development and outcome of the diseases, including disease complications. Immunomodulatory treatment has demonstrated greatly improved efficacy in moderate to severe disease activity. The long-term effect on the natural course of disease and sustained reduced burden on society over many years require study. This article summarizes recent knowledge on factors influencing the natural history of IBD, including the impact of treatment. Increased understanding of disease mechanisms is needed as a basis for new treatment strategies in the future.

Introduction

A direct relationship exists between the duration of inflammatory bowel disease (IBD) and the burden of complications. This burden is related to general disability from disease activity or localized organic complications, treatment-related side effects, and problems related to surgery and hospitalizations. The impact of IBD on costs is high in many countries [1,2]. The total burden of IBD on society in the United States and worldwide [3] and time trends of US hospital utilization from 1970 to 2004 [4] were investigated recently. Disease activity was predictive of reduced health-related quality of life (QoL) [5]. Specific problems are related to IBD in pregnancy and childhood.

In addition to these common and specific problems, disease manifestation varies greatly, which necessitates primarily discussion of natural history. A better understanding of the natural history and course of disease will also help us to differentiate between patients with a good and poor prognosis. The connection between natural history and complications is related to aggressiveness and duration of disease. The ultimate question today is whether new treatments may change the natural history of disease and significantly reduce complications, need for surgery, and hospitalizations. Extraintestinal manifestations quite often represent the main treatment goal for patients, and very often with disease activity independent of the intestinal activity. They demand early and sustained treatment over many years. Gastrointestinal fistulas, which represent a more integrated part of the intestinal activity, are discussed in this article along with specifically defined clinical topics.

Natural History

Disease incidence and prevalence

Because the incidence rate of IBD has increased over the past decades—first in Europe, then in the United States, and later in developing countries—industrialization seems to be an environmental prerequisite for the increasing incidence, harboring the most important environmental elements behind the start of the natural history of disease. Because the diseases are lifelong, the burden of treatment and disability are cumulative, with long-term individual problems and increasing demands for resources on the society. It is important to achieve a better understanding of the complexity of risk factors in modern society that might be a part of the cause relationships of IBDs.

Geographic variations

Epidemiologic surveys have generally supported Westernized life style as a risk factor of IBD. A north-south gradient for incidence rate, phenotype, and recurrence was demonstrated in Europe [6–8] and an east-west gradient in Canada [9]. In Europe, Crete is the exception, with an incidence of Crohn's disease (CD) comparable to northern Europe.

The ratio between CD and ulcerative colitis (UC) has also shown geographic variations. UC seems more common than CD in industrialized countries of northern

areas of western Europe [6], unlike Canada [9]; however, this UC/CD difference is less prominent in southern Europe. In northern France, the opposite seems to be the case [6], with a higher incidence rate for CD than for UC; because this prevalence also seems to be the case for southern Germany [10], we may no longer describe this as a French enigma, but perhaps as a tendency for middle Europe. Regarding gender, 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 the age of puberty [11].

Environmental factors

The hygiene hypothesis [12], which indicated reduced microbiologic diversity [13] as a common factor in modern society, is now considered the most important environmental factor causing increased incidence of disease. Additionally, possible specific pathogenic bacteria or commensal bacteria omitting the immunocompromised cells may serve as explanations for the development of disease [12].

A reduced diversity of intestinal bacteria seems to be related to living in the northern hemisphere [14]. This also seems to fit with a generally increased risk for IBD among people living in the north, which might be explained mainly by industrialization. However, latitude might be an independent risk factor related to general global variations (eg, sun exposure and reduction in vitamin D) [15].

In addition to reduced diversity and genetically reduced mucosal barrier with a compromised innate immune system, a third risk factor might be necessary for the microbial action that turns this imbalance into a chronic state. However, it is also possible that other endogenous or even extracorporal factors might be important. A recent report on a significant association between the concentration of iron in drinking water and IBD (both CD and UC) might be explained by effects of iron on virulence or growth of microbes, an action previously well known by microbiologists, or by oxidative stress [16]. Future studies may clarify this question.

Smoking is generally accepted as a risk factor in CD and for worsening the disease course (eg, reduced response to treatment, increased relapse rate, and complications) [17], However, in UC, smoking has a protective effect against the same outcomes of disease [8].

The connection between smoking and disease onset is less clear, but a metaanalysis showed an OR of 0.58 for UC and 1.76 for CD among smokers [18] 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 [19]. Moreover, a recent investigation suggested passive smoking was detrimental for the outcome of CD patients [20]. A possible relationship between age at diagnosis and smoking was also suggested [21].

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 [22]. 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 (eg, a result of disease activity or exposure to treatment) [23].

Genetic factors

Much understanding of genetic mechanisms in IBD was derived from the high frequency of concordant disease among monozygotic twins in CD [24]. Having a family member with IBD is a well-known risk factor for developing IBD. Familial cases are younger at diagnosis compared with sporadic cases, a finding ascribed to genetic anticipation [25]. Our knowledge about the outcome of familial disease is hampered by the lack of follow-up over time; in addition, a clear relationship between disease severity and familial disease, which might reflect the complicated interplay between genetic and environmental factors, has not been established [26]. Future research in epigenetics may disclose new explanations for the natural history of individual disease regarding the interplay between inheritance and environmental factors [27•].

The *NOD2* mutation seems to play an important role in the determination of disease phenotype, as mostly related to ileal and fibrostenotic disease [28]. 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 must be regarded as responsible for the disease activity of an individual. In the future, the immune system will represent the target for early individual treatment strategy on diverse genes at different levels, such as innate immunity, antigen presentation molecules, epithelial integrity, drug transporter, and cell adhesion [29].

CD is generally considered to be more genetically disposed than UC. However, a recent large European study demonstrated for the first time, based on defective interleukin-10 function, that genetic susceptibility is important for the development of UC [30•].

Disease presentation

Age peaks for onset of disease appear for CD between 15 and 25 years of age, and for UC between 25 and 35 years, and demonstrate an anticipated burden of long duration for these lifelong diseases, in which reduced overall survival is questionable [31,32]. Moreover, young age at onset is associated with primary complicated disease, which calls for immediate and long-term demands for health-care resources.

At onset, the diseases may show a variety of phenotypes regarding symptoms, disease distribution, and degree of activity. Time from onset of symptoms to diagnosis is usually less than 1 year both in adults and children [11,33] but may vary greatly, especially in association with vague symptoms, and may extend to several years. To what extent the time lag of diagnosis may affect response to treatment is not settled, but it is expected that in many cases, early irreversible changes may occur before medication is induced, whereby the patient might be primarily refractory to treatment.

Disease course

A purely natural course of disease is impossible to account for in IBD because all patients are subjected to treatment from time of diagnosis. Disease course therefore depends on choice of medication and the patient's response to treatment. On the other hand, based on our experience, some features regarding disease course may seem unrelated to treatment. Such features are change in disease distribution, tendency of relapse, tendency of reoperations, and secondary fistulas. Therefore, it is important to recognize that about half the patients in a population-based study did not require glucocorticosteroid (GCS) during the first year of disease [33]. A further reduction in the number of patients treated with systemic corticosteroids and 5-aminosalicylic acid was shown from the first to the second 5-year period [34].

In UC, further extension of disease from proctitis or left-sided colitis to substantial or total colitis has been reported over the first few years of disease [35]. The significance of this progression on disease outcome is under debate. In prospective population-based studies, a tendency of relapse seems to continue over at least 10 to 20 years [36], although reduced disease activity over time and even burnout of disease in a subgroup of patients [37] were discussed. In a recent study including 10-year follow-up after diagnosis, a significantly reduced disease activity during the second compared with the first 5-year period was demonstrated in CD, even before biologic treatment was introduced. However, the same study showed a cumulative increased relapse rate, and that repeated individual need for surgery and secondary fistulas are continuous problems during the entire period [17]. These results may emphasize the importance of differentiating between early low and increased risk of a complicated course of disease.

Individual change of diagnosis—among CD, UC, and IBD unclassified (IBDU)—has been reported in about 10% of patients during the first year after diagnosis [35]. In contrast, most IBDU cases seem to be classified as UC or CD within 5 years after diagnosis [35,38].

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 [39] compared with previous experience. However, this reduction has not been observed over the long term in CD [17].

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 [40]. The rate of disabling disease within 5 years was reported to be 58%, and the rate of severe disease 37%, with stricturing disease and weight loss at diagnosis representing independent risk factors [41]. Another hospital-based study showed that 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 [42].

Impact of treatment

After introduction of immunomodulatory medication in IBD, we have observed improved and more sustained response to treatment. In the short run, it may be claimed that any effective medication acts on the natural course of disease. However, even more important is the question of whether improved treatment will change the natural course of disease over time. This question must be judged on the basis of long-term follow-up data, based on prospective longitudinal studies using clinically important criteria, such as relapse rate and frequency of complications, surgery, reoperations, and hospitalizations. For society, burden of disease related to health economy and cost utility records is important.

Relapse rate and conventional treatment

A recent prospective study showed a 10-year cumulative relapse rate of 90% over 10 years after diagnosis in CD, based on conventional treatment [17], in keeping with the results of a recent European study [7].

In UC, recent population-based studies showed a high cumulative probability of relapse over 10 years [8,34]. The patients using GCS during the first 5-year period showed a higher relapse rate and a subsequent higher need of GCS during the second 5-year period.

The cumulative high relapse rate for both CD and UC, and the sustained need for steroids in a subgroup of nonoperated patients, demonstrates a suboptimal effect of previous conventional treatment on the natural course of IBD.

Effect of azathioprine

Whereas population-based studies with individual treatment included only a small proportion of patients treated with azathioprine, a recent study showed that withdrawal of azathioprine in patients who had been in remission for at least 3.5 years was not equivalent to being kept on treatment with the same drug [43]. This suggests that azathioprine in CD is at least partly able to change the natural course of disease over this period of time.

Relationship to surgery

Recent population-based studies showed a comparatively lower frequency of surgery in CD compared with hospital-based studies, with the highest frequency during the first 2 years but still with an increased cumulative risk of surgery

over 10 years [7,17]. A highly significant relationship was found between initial location in the ileum or proximal disease with stenotic and penetrating disease as well as a relationship to age at diagnosis below 40 years, which is also in keeping with previous hospital-based studies. The fact that the highest frequency of surgery appears during the early stage of disease represents an important challenge to early adequate medical treatment. Moreover, a recent meta-analysis failed to detect any specific risk factors for reoperations among postoperative patients treated with placebo [44]. This finding could imply that early effective medication represents a general solution to previously refractory and relapsing cases. Nevertheless, the report of a prolonged effect of primary surgery at diagnosis suggests that a role still exists for this mode of treatment in subgroups of patients, especially in ileal and complicated disease [42].

In UC, recent population-based studies showed a colectomy rate less than 10% during a 10-year prospective follow-up period—much lower than previously reported, especially from referral centers [39]. Chronic activity and increasing extent of disease over time may seem important risk factors for later surgery in UC [39]. Appendectomy and smoking had additive beneficial effects on frequency of surgery in UC [45]. The reasons for reduced frequency of surgery may be explained by differences between population-based and hospital-based series.

Obviously, important differences exist between the treatment policies of different treatment centers, as evident from the impressive differences between comparable centers in northern Europe with regard to the frequency of surgery in the same study [39]. Nevertheless, based on the significantly reduced operation rate in southern Europe, one should not overlook the possibility of a different natural history or natural course of disease, which may result from geographic, cultural, or strictly microbial differences between populations. However, the consistent finding over time that frequency of surgery is highest during the first few years after diagnosis again focuses on the importance of early adequate medical intervention for UC.

Pediatric problems

Childhood onset of IBD is characterized by extensive intestinal involvement, including ileum and colon in most cases with CD, and total colitis in UC [46]. A rapid early progression was reported in CD, with about one third of patients demonstrating complicated disease at diagnosis, including proximal disease [11], and with about two thirds showing complicated disease at the seventh year of follow-up [11]. A different immunologic expression during childhood, on the basis of a genetically transformed innate immune system, may explain the different clinical phenotypes among adults and children with IBD [47]. An interesting shift from male to female predominance around the age of puberty is unclear. An additional important therapeutic problem is represented by the tendency of growth retardation and nutritional problems. All these problems in childhood represent a challenge to early adequate therapeutic intervention.

Problems related to pregnancy

The effect of IBD on pregnancy seems to rely on disease activity at the time of conception and whether remission persists during pregnancy. Reduced fertility and fecundity have been discussed, but the most solid data are derived from previously operated females with IBD. Population-based studies have demonstrated an overall tendency of preterm birth. A recent large cohort study showed that women with IBD are more likely to have an adverse outcome related to pregnancy [48]. Disease activity and medical treatment did not predict adverse outcomes.

Except for the contraindications related to certain IBD drugs (eg, metronidazole and methotrexate) during pregnancy, it is generally agreed that the disease is a greater risk factor for the offspring than the use of medication. Consequently, the main goal for treatment during pregnancy is to stay in remission or to keep the disease activity under control. In a recent case-control study with high-dose treatments of GCS or cyclosporine, even treatment for serious UC during pregnancy was successful without serious complications for pregnancy outcome [49]. Moreover, the most recent reports (unpublished) on biologic treatment have not provided any proof that these drugs are harmful to the offspring, whereas uncertainty still exists regarding the significance of the sustained antitumor necrosis factor (TNF) antibody titer during the first year of life [50].

Regarding the effect of pregnancy on IBD, several limited reports have been published of relapses during pregnancy, including trimester-related tendency of relapse and relapses in the perinatal period. No large series have settled these questions; data are needed and controlled studies are under way.

Cancer risk in IBD

Evidence exists for an increased risk of cancer in UC and CD, with a much lower age of cancer diagnosis than for sporadic colorectal cancer in the general population [51,52]. Specific risk factors are the coexistence of primary sclerosing cholangitis (PSC) and familial cancer, and in general, the disease activity seems to increase the risk of cancer. The effect of anti-inflammatory treatment as prophylaxis against cancer in IBD is not settled.

A recent metaanalysis of risk of malignancy in IBD patients treated with immunosuppressives did not show an increased risk compared with patients not receiving such treatment [53]. Regarding biologic treatment, no long-term follow-up has showed an increased risk compared with patients devoid of such treatment.

Effect of biologic treatment

With the introduction of anti-TNF therapy, a new era of treatment for IBD was entered and a new basis was formed for experience regarding IBD in complicated disease. The first phase 3 trial with anti-TNF showed a prolonged effect of treatment in a substantial number of patients with moderate to severe disease activity. The sustained effect over 52 weeks was seen mainly in patients

who were primary responders to the treatment [54]. A similar and significant effect was also shown for fistulizing disease during 52 weeks of treatment [55].

After the first trials of anti-TNF therapy, several biologics were introduced. Their introduction resulted in a greater number of treatment options and increased experience of greatly improved early efficacy for a substantial minority of patients with CD. One of the finished trials reports on prolonged efficacy over 108 weeks for 83% of the primary responders and with a steroid-free remission over years [56]. The study also showed sustained improvement in QoL, including significant improvement in complications (eg, fistulas).

In UC, a substantial effect of anti-TNF treatment was established in chronic active disease and treatment-refractory cases [57] and in severe disease [58] as an alternative to treatment with cyclosporine. The need for more effective treatment in UC may be even more emphasized by data reporting a substantial frequency of complications and need for reoperations during long-term follow-up of surgical resections [59].

Extraintestinal Manifestations and Rare Complications

Extraintestinal manifestations (EIM) are strongly related to IBD regarding pathogenetic mechanisms and therapeutic options; when present, EIMs represent a main target for active treatment. The most important EIMs are PSC, ankylosing spondylarthritis (AS), pyoderma gangrenosum (PG), uveitis/iritis, and erythema nodosum. In a large population-based study, 6.2% of IBD patients showed extraintestinal manifestations [60]. The most frequent manifestation among men was PSC, reported in 3.0% of cases (most commonly in UC), whereas uveitis/iritis was most common among women with 3.8% (most commonly in UC). The other manifestations were seen in 1.2% to 2.9% of cases, and only 0.3% of patients had multiple manifestations.

During long-term follow-up over 15 years, 39% of patients under active follow-up demonstrated evidence of sacroiliitis on MRI and 12% fulfilled the criteria for AS [61]. HLA-B27 conveyed a high risk for developing axial inflammation in IBD.

In another recent study, the prevalence of erythema nodosum was found to be 7.4% and PG was 2.3% [62]. The former was significantly more frequent in CD and showed a relationship to disease activity and arthritis. A relationship was also found between PG and both arthritis and uveitis.

In a large pediatric cohort, 6% had at least one EIM before the diagnosis of IBD, and 29% at least one EIM within 15 years of diagnosis, with a higher rate among older children at diagnosis [63]. Arthritis (26%) and aphthous stomatitis (21%) were most common. Arthritis (17%) and osteopenia/osteoporosis (15%) were most commonly seen during the period after diagnosis. No relationship to type of IBD or race/ethnicity was found.

A recent review shed further light on the EIMs in pediatric IBD and supports the strong relationship between complications and IBD appearing early in life, and a relationship to duration of disease [64].

Several other complications were reported in association with IBD, such as thromboembolism and vascular complications, airway and renal complications, and central nervous system complications, which all appear in less than 1% of cases in the long term [65].

Conclusions

The understanding of the natural history of IBD has increased tremendously during the past decade because of parallel increases in knowledge of clinical epidemiology, molecular biology, and pharmacology. The recent reduction in hospitalization and surgery after introduction of anti-TNF therapy gives hope for the future of patients with IBD and for reduced burden on society. However, the fact that only one third of moderate to severe cases maintain complete remission on any biologic treatment may require different strategies to interact with the natural history of IBD. Long-term follow-up over 10 to 20 years will reveal how the present biologics have changed the natural course of disease for patients with moderate to severe and complicated disease. Moreover, the total burden of IBD must be assessed in longitudinal studies for all new therapeutic agents. The challenge for the future is to further understand the interplay between genes and cellular expression as a basis for more effective and safe drug compounds. The introduction of epigenetic factors in research may represent a new paradigm for understanding this interplay. More emphasis on translational research will shed light on our understanding of the mechanisms of disease, which will further improve our treatment strategies. We can expect an increasing variation in clinical phenotypes related to geographic differences with the increase of IBD in developing countries, which implies a demand for more international networks in translational research.

Disclosure

Dr. Vatn is a member of the advisory board for Abbott, and was invited for an interview by Schering-Plough regarding the 10-year anniversary of Remicade.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Kappelman MD, Sheryl L, Porter CQ, et al.: **Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults.** *Gastroenterology* 2008, **135:**1907–1913.
2. Odes S, Vardi H, Friger M, et al.: **Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation.** *Gastroenterology* 2006, **131:**719–728.

3. Everhart JE, Ruhl CE: **Burden of digestive diseases in the United States part II: lower gastrointestinal diseases.** *Gastroenterology* 2009, **136:**741–754.
4. Sonnenberg A: **Hospitalization for inflammatory bowel disease in the United States between 1970 and 2004.** *J Clin Gastroenterol* 2009, **43:**297–300.
5. Bernklev T, Jahnsen J, Aadland E, et al.: **Course of disease, drug treatment and health related quality of life in patients with inflammatory bowel disease 5 years after initial diagnosis.** *Eur J Gastroenterol Hepatol* 2005, **17:**1037–1045.
6. Shivananda S, Lennard-Jones J, Logan R, 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:**690–697.
7. Wolters F, Russel MG, Sijbrandij J, et al.: **Phenotype at diagnosis predicts recurrence rates in Crohn's disease.** *Gut* 2006, **55:**1124–1130.
8. Hoie O, Wolters F, Riis L, 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.
9. Bernstein CN, Wajda A, Svenson LW, et al.: **The epidemiology of inflammatory bowel disease in Canada: a population-based study.** *Am J Gastroenterol* 2006, **101:**1559–1568.
10. Ott C, Obermaier F, Thieler S, et al.: **The incidence of inflammatory bowel disease in a rural region of southern Germany: a prospective population-based study.** *Eur J Gastroenterol Hepatol* 2008, **20:**917–923.
11. Vernier-Massouille G, Balde M, Salleron J, et al.: **Natural history of pediatric Crohn's disease: a population-based cohort study.** *Gastroenterology* 2008, **135:**1106–1113.
12. Guarner F, Bourdet-Sicard R, Brandtzaeg P, et al.: **Mechanisms of disease: the hygiene hypothesis revisited.** *Nat Clin Pract Gastroenterol Hepatol* 2006, **3:**275–284.
13. Ley R, Peterson D, Gordon J: **Ecological and evolutionary forces shaping microbial diversity in the human intestine.** *Cell* 2006, **124:**837–848.
14. Hildebrand H: **On the generality of the latitudinal diversity gradient.** *Am Nat* 2004, **163:**192–211.
15. Hayes CE, Nashold FE, Froicu M, et al.: **The immunological functions of the vitamin D endocrine system.** *Cell Mol Biol (Noisy-le-grand)* 2003, **49:**277–300.
16. Aamodt G, Bukholm G, Jahnsen J, et al.: **The association between water supply and inflammatory bowel disease based on a 1990–1993 cohort study in southeastern Norway.** *Am J Gastroenterol* 2008, **168:**1065–1072.
17. Solberg IC, Vatn MH, Hoie O, et al.: **Clinical course in Crohn's disease: results of a population-based ten-year follow-up study.** *Clin Gastroenterol Hepatol* 2007, **5:**1430–1438.
18. Mahid SS, Minor KS, Soto RE, et al.: **Smoking and inflammatory bowel disease: a meta-analysis.** *Mayo Clin Proc* 2006, **81:**1462–1471.
19. Russel RK, Farhodi R, Wilson M, et al.: **Perinatal passive smoke exposure may be more important than childhood exposure in the risk of developing childhood IBD.** *Gut* 2005, **54:**1500–1501.
20. van der Heide F, Dijkstra A, Weersma RK, et al.: **Effects of active and passive smoking on the disease course of Crohn's disease and ulcerative colitis.** *Inflammatory Bowel Dis* 2009, **15:**1199–1207.
21. Regueiro M, Kevin EK, Onki C, et al.: **Cigarette smoking and age at diagnosis of inflammatory bowel disease.** *Inflamm Bowel Dis* 2005, **11:**42–47.
22. Bridger S, Lee JCW, Bjarnason I, et al.: **Inflammatory bowel disease. In siblings with similar genetic susceptibility for inflammatory bowel disease, smokers tend to develop Crohn's disease and non-smokers develop ulcerative colitis.** *Gut* 2002, **51:**21–25.
23. Hoie O, Aamodt G, Vermeire S, et al.: **Serological markers may predict disease course in ulcerative colitis. A study in an unselected population-based cohort followed for 10 years.** *J Crohn's Colitis (JCC)* 2008, **2:**114–122.
24. Halfvarson J, Bodin L, Tysk C, et al.: **Inflammatory bowel disease in a Swedish cohort. A long-term follow up of concordance and clinical characteristics.** *Gastroenterology* 2003, **24:**1767–1773.
25. Satsangi J, Grootsholten L, Holt H, et al.: **Clinical patterns of familial inflammatory bowel disease.** *Gut* 1996, **38:**738–741.
26. Bengtson M-B, Solberg IC, Aamodt G, et al.: **Clustering in time of familial IBD separates ulcerative colitis from Crohn's disease.** *Inflamm Bowel Dis* 2009 (Epub ahead of print).
27.• Slatkin M: **Epigenetic inheritance and the missing heritability problem.** *Genetics* 2009, **182:**845–850.
This article describes a new model for calculation of missed inheritance within epigenetics, addressing the problem of genetic versus epigenetic inheritance in IBD. It also discusses multidisciplinary questions of epigenetics in the literature.
28. Abreu MT, Taylor KD, Lin YC, et al.: **Mutations in NOD 2 are associated with fibrostenotic disease in patients with Crohn's disease.** *Gastroenterology* 2002, **123:**679–688.
29. Strober W, Fuss I, Mannon P: **The fundamental basis of inflammatory bowel disease.** *J Clin Invest* 2007, **117:**514–521.
30.• Franke A, Belchun T, Karlsen TH, et al.: **Sequence variants in IL10, ARPC2 and multiple other loci contribute to ulcerative colitis susceptibility.** *Nat Genet* 2009, in press.
This article provides the first documentation on genome-wide association to UC susceptibility, showing sequence variants in IL10. This study is a large-scale effort of comprehensive genome-wide methodology on several large international materials.
31. Wolters FL, Russel MG, Sijbrandij J, et al.: **Crohn's disease: increased mortality 10 years after diagnosis in a European-wide population-based cohort.** *Gut* 2006, **55:**510–518.
32. Hoie O, Schouten LJ, Wolters FL: **Ulcerative colitis: no rise in mortality in a European-wide population-based cohort 10 years after diagnosis.** *Gut* 2007, **56:**497–503.
33. Moum B, Ekbom A, Vatn MH, et al.: **Clinical course during the first year after diagnosis in ulcerative colitis and Crohn's disease.** *Scand J Gastroenterol* 1997, **32:**1005–1012.
34. Solberg IC, Lygren I, Jahnsen J, et al.: **Clinical course during the first teten years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study).** *Scand J Gastroenterol* 2009, **44:**431–440.
35. Henriksen M, Jahnsen J, Lygren I, et al.: **Change of diagnosis during the first years after onset of inflammatory bowel disease: results of a prospective follow up study (the IBSEN study).** *Scand J Gastroenterol* 2006, **41:**1037–1043.
36. Langholz E, Munkholm P, Davidsen M, et al.: **Course of ulcerative colitis: analysis of change in disease activity over years.** *Gastroenterology* 1994, **107:**3–11.
37. Munkholm P, Langholz E, Davidsen M, et al.: **Disease activity courses in a regional cohort of Crohn's disease patients.** *Scand J Gastroenterol* 1995, **30:**699–707.
38. Geboes K, Colombel JF, Greenstein A, et al.: **Indeterminate colitis: a review of the concept—what is in a name?** *Inflamm Bowel Dis* 2008, **14:**850–857.
39. Hoie O, Wolters FL, Riis L, et al.: **Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years.** *Gastroenterology* 2007, **132:**507–515.
40. Beaugerie L, Seksik P, Nion-Larmurier I: **Predictors of Crohn's disease.** *Gastroenterology* 2006, **130:**650–656.
41. Loly C, Belaiche J, Louis E: **Predictors of severe Crohn's disease.** *Scand J Gastroenterol.* 2008, **43:**948–954.
42. Latella G, Cocco A, Angeluchi A, et al.: **Clinical course of Crohn's disease first diagnosed at surgery for acute abdomen.** *Dig Liver Dis* 2009, **41:**269–276.
43. Lemann M, Mary J-Y, Colombel JFA: **A randomized double blind controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine.** *Gastroenterology* 2005, **128:**1812–1818.
44. Renna S, Camma C, Modesto I, et al.: **Meta-analysis of the placebo rates of clinical relapse and severe endoscopic recurrence in postoperative Crohn's disease.** *Gastroenterology* 2008, **135:**1500–1509.

45. Cosnes J, Carbonell F, Beaugerie L, et al.: **Effects of appendicectomy on the course of ulcerative colitis.** *Gut* 2002, **51:**803–807.
46. van Limbergen J, Russel RK, Drummond HE, et al.: **Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease.** *Gastroenterology* 2008, **135:**1114–1122.
47. Perminow G, Reikvam DH, Lyckander LG, et al.: **Increased number and activation of colonic macrophages in pediatric patients with untreated Crohn's disease.** *Inflamm Bowel Dis* 2009, **15:**1368–1378.
48. Mahadevan U, Sandborn WJ, Li DK, et al.: **Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California.** *Gastroenterology* 2007, **133:**1106–12.
49. Reddy D, Murphy SJ, Kane SV: **Relapses of inflammatory bowel disease during pregnancy: in-hospital management and birth outcomes.** *Am J Gastroenterol* 2008, **103:**1203–1209.
50. Mahadevan-Velayos U, Martin C, Sandler R, et al.: **PIANO. Pregnancy in inflammatory bowel disease and neonatal outcomes: a national prospective registry**. *Presented at Digestive Disease Week*. Chicago; May 30–June 4, 2009.
51. Bernstein CN, Blanchard JF, Kliewer E: **Cancer risk in patients with inflammatory bowel disease. A population-based study.** *Cancer* 2001, **91:**854–862.
52. Brackmann S, Andersen SN, Aamodt G, et al.: **Two distinct groups of colorectal cancer in inflammatory bowel disease.** *Inflamm Bowel Dis* 2009, **15:**9–16.
53. Masunuga Y, Ohuo K, Ogawa R: **Meta-analysis of risk of malignancy with immunosuppressive drugs in inflammatory bowel disease.** *Ann Pharmacother* 2007, **41:**21–28.
54. Hanauer SB, Feagan BG, Lichtenstein GR, et al.: **Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial.** *Lancet* 2002, **359:**1541–1549.
55. Sands B, Anderson FH, Bernstein CN, et al.: **Infliximab maintenance therapy for fistulizing Crohn's disease.** *N Engl J Med* 2004, **350:**876–985.
56. Kamm MA, Hanauer SB, Pannachione R, et al.: **Steroid-free remission in patients with Crohn's disease who received adalimumab therapy for at least 3 years: long-term results from CHARM**. *Poster presented at 4th Congress of the European Crohn's and Colitis Organization*. Hamburg, Germany; February 5–7, 2009.
57. Rutgeerts P, Sandborn WJ, Feagan BG, et al.: **Infliximab for induction and maintenance therapy for ulcerative colitis.** *N Engl J Med* 2005, **353:**2462–2476.
58. Jarnerot G, Hertervig E, Friis-Liby I, et al.: **Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized placebo-controlled study.** *Gastroenterology* 2005, **128:**1805–1811.
59. Dhillon S, Loftus EV, Tremaine WJ, et al.: **The natural history of surgery for ulcerative colitis in a population-based cohort from Olmsted County, Minnesota [abstract 819].** *Am J Gastroenterol* 2005, **100:**S303.
60. Bernstein CN, Blanchard JF, Rawsthorne P, et al.: **The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study.** *Am J Gastroenterol* 2001, **96:**116–122.
61. Orchard TR, Holt H, Bradbury L, et al.: **The prevalence, clinical features and association of HLA-B27 in sacroiliitis associated with established Crohn's disease.** *Aliment Pharmacol Ther* 2009, **29:**193–197.
62. Yuksel I, Basar O, Ataseven H, et al.: **Mucocutaneous manifestations in inflammatory bowel disease.** *Inflamm Bowel Dis* 2009, **15:**546–550.
63. Jose FA, Garnett EA, Vittinghoff E, et al.: **Development of extraintestinal manifestations inpediatric patients with inflammatory bowel disease.** *Inflamm Bowel Dis* 2009, **15:**63–68.
64. Jose FA, Heyman MB: **Extraintestinal manifestations of inflammatory bowel disease.** *J Pediatr Gastroenterol Nutr* 2008, **46:**124–133.
65. Papa A, Scaldaferri F, Danses S, et al.: **Vascular involvement in inflammatory bowel disease: pathogenesis and clinical aspects.** *Dig Dis* 2008, **26:**149–155.