World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i1.31

World J Gastroenterol 2014 January 7; 20(1): 31-36
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (3): Inflammatory bowel disease

Natural history and long-term clinical course of Crohn's disease

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Received: October 10, 2013 Revised: November 7, 2013
Accepted: November 12, 2013
Published online: January 7, 2014

Abstract

Crohn's disease is a chronic inflammatory disease process involving different sites in the gastrointestinal tract. Occasionally, so-called metastatic disease occurs in extra-intestinal sites. Granulomatous inflammation may be detected in endoscopic biopsies or resected tissues. Genetic, epigenetic and environmental factors appear to play a role. Multiple susceptibility genes have been described in both familial and non-familial forms while the disease is phenotypically heterogeneous with a female predominance. The disorder occurs over a broad age spectrum, from early childhood to late adulthood. More than 80% are diagnosed before age 40 years usually with terminal ileal and colonic involvement. Pediatric-onset disease is more severe and more extensive, usually with a higher chance of upper gastrointestinal tract disease, compared to adult-onset disease. Long-term studies have shown that the disorder may evolve with time into more complex disease with stricture formation and penetrating disease complications (*i.e.*, fistula, abscess). Although prolonged remission may occur, discrete periods of symptomatic disease may re-appear over many decades suggesting recurrence or re-activation of this inflammatory process. Eventual development of a cure will likely depend on identification of an etiologic cause and a fundamental understanding of its pathogenesis. Until now, treatment has focused on removing risk factors, particularly cigarette smoking, and improving symptoms. In clinical trials, clinical remission is largely defined as improved numerical and endoscopic indices for "mucosal healing". "Deep remission" is a conceptual, more "extended" goal that may or may not alter the long-term natural history of the disease in selected patients, albeit at a significant risk for treatment complications, including serious and unusual opportunistic infections.

Key words: Natural history; Crohn's disease; Age-dependent phenotypes

Core tip: Crohn's disease remains an intriguing heterogeneous disorder characterized by a granulomatous inflammatory process. The phenotypic clinical expression of Crohn's disease is clearly age-onset dependent as most children and adolescents suffer more severe, more extensive and more complicated disease than most adults, and the elderly. If evaluated over a long period of time, the disease appears to be progressive, but only intermittently active, with some appearing to have prolonged periods of sub-clinical disease and others expressing complex disease with stricture formation and penetrating complications, even at the time of initial clinical presentation. Although the precise cause of Crohn's disease remains a mystery, an increasing appreciation for the long-term natural history may permit development of more effective treatment regimens. Ultimately, however, both clinical and fundamental investigative efforts should focus on discovering the cause of the disorder since this approach may offer the best opportunity for cure.

Freeman HJ. Natural history and long-term clinical course of Crohn's disease. *World J Gastroenterol* 2014; 20(1): 31-36

Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i1/31.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i1.31

INTRODUCTION

Crohn's disease is a chronic inflammatory disorder that usually involves different sites along the length of the gastrointestinal tract, and also, occasionally, other extra-intestinal "metastatic" sites. Genetic, epigenetic and environmental factors are believed to play a role in its etiology and pathogenesis[1,2]. Indeed, recent evidence suggests that multiple susceptibility genes may be present and play a critical role[1,2]. Some believe that genetic risk profiling to predict the eventual disease course is feasible[3,4]. Currently, it is thought that the disorder is likely related to an aberrant immunological response to intestinal microbiota in genetically-susceptible individuals[5]. A prevalence of up to 1% has been recorded with numerous studies suggesting that the incidence is increasing in developed or industrialized as well as developing or non-industrialized countries[6]. Although there is little epidemiologic data, a recent analysis noted that the rise in incidence and prevalence over time and in different regions around the world reflects emergence as a global disease[6]. A key pathological footprint of Crohn's disease is the granulomatous inflammatory response, a special form of chronic inflammation characterized by focal collections of macrophages, epithelioid cells and multinucleated giant cells. It is believed that initiation and development of this specific form of inflammatory reaction depends on persistence of the inciting agent, a complex immune reaction to perpetuate the granulomatous response leading to development of necrosis and fibrosis[7].

The clinical expression of Crohn's disease is known to be very heterogeneous. Prior working groups for the World Congress of Gastroenterology in Vienna and later in Montreal developed a classification scheme that has evolved[8,9]. An important goal was to enumerate different phenotypic characteristics so that more homogeneous cohorts could be explored and compared, particularly for geographically-distinct populations. Application of this classification schema to a tertiary care clinical database revealed a female predominance, occasional familial nature, and a high rate of stricture formation and penetrating disease complications[10,11].

Crohn's disease appears to be a life-long disorder becoming clinically apparent at almost any time from early childhood to late adulthood[10,11]. For most, the actual onset of the disease, or more precisely, age of detection or diagnosis, has usually been during the late teens and early twenties, and now, during the past two or three decades, over 80% of patients with Crohn's disease are diagnosed before age 40 years[10]. Moreover, the majority have involvement primarily of the ileum and colon, at least based on the most sensitive and most modern imaging methods[10,11]. Finally, most clinicians usually evaluate and treat "late" complicated disease, while "early" disease without stricture or fistula development may not be as commonly seen, particularly in tertiary-care centers.

ONSET OF DISEASE AND DIAGNOSIS

Clearly, an appreciation for the natural history of Crohn's disease must depend, not on the age at diagnosis defined by these classifications, but the actual time of onset of the disorder. These are obviously very different. Indeed, some authorities have opined that symptoms may be chronically present over a long latent period in many patients for months, even years, before a diagnosis is entertained and established. Symptoms that eventually lead the patient to specialist referral include diarrhea, abdominal pain and weight loss, but these are not always universally present. Occasionally, only a single symptom, possibly abdominal pain alone, may be evident. In some, suspected appendicitis may first lead to detection of an unexpected ileal inflammatory process. For others, extra-intestinal findings (*e.g.*, arthropathy or a skin disorder, such as erythema nodosum) may be present without significant abdominal symptoms. Or, rarely, granulomatous inflammatory change defined in an extra-intestinal site, called metastatic Crohn's disease, including skin, muscle, or bone may complicate or actually lead to recognition of occult intestinal disease[12-14]. For metastatic disease, a distinct focus of granulomatous inflammatory disease is defined, geographically separated from the gastrointestinal tract. Other "systemic" or distant sites may also be involved in patients with Crohn's disease leading to atypical clinical features, such as a concomitant sellar inflammatory mass[15], or even unusual complications, sometimes attributed to treatment, such as osteonecrosis[14].

In Crohn's disease, the initiating event (including, a possible infectious agent) leading to this ongoing, stepwise and destructive inflammatory process may no longer be detectable, having long departed the scene. Indeed, multiple events (or agents) could conceivably precipitate or generate this insidious inflammatory cascade causing eventual symptoms and signs at the bedside as well as end-pathological changes in the laboratory, clinically recognized as Crohn's disease. Additional studies are urgently needed to further elucidate these hypothetical genetic, microbiologic and immunologic factors that permit progression of this frustrating clinical disorder.

DISEASE EXTENT AND LOCALIZATION

In Crohn's disease, there is a predilection for the distal small intestine and proximal colon[8-11]. Of course, more extensive involvement of the intestinal tract may also occur[16] and the old adage that Crohn's disease can potentially involve any site "from mouth to anus" still holds true, although this probably deserves to be altered slightly to "and in other sites separated from the gastrointestinal tract as metastatic Crohn's disease". Familial factors play a role in Crohn's disease[17], including genetic factors that appear to directly influence the localization

of the disease in different intestinal sites[18,19]. Further information, however, is clearly required on fundamental luminal and intestinal factors that play a role in localization of the disorder to specific sites along the length of the gastrointestinal tract.

Crohn's disease may develop in the upper gastrointestinal tract, often with concomitant disease in the ileum, colon, or elsewhere. Rarely, at least in Caucasian populations, the disorder may also occur solely in the upper gastrointestinal tract without disease involvement elsewhere[9-11]. Interestingly, a recent study from Hong Kong suggested that the Chinese may have an increased risk for this upper gastrointestinal tract phenotype[20]. Also, extensive jejuno-ileal disease, evaluated over the long-term, appears to reflect a form of Crohn's disease that historically responds poorly to medications, often leading to surgical treatment, long-term nutritional support and greater costs for care[13,20,21]. New and developing biological treatment paradigms largely focused on reducing numerical activity indices in ileocolonic disease may have little impact here, unless the long-term severity and extent of the inflammatory process can be reduced. In recent years, improved and novel imaging methods have also opened the door to more precise recognition of this extensive small intestinal group[22], so that early inflammatory changes may be detected along the length of the small intestine, rather than late-stage and more complex disease.

DISEASE BEHAVIOR

Crohn's disease is a chronic, persistent and destructive disorder with different forms of clinical behavior[23,24]. Over the long term, the disease appears to be progressive although the rate of progression may be altered or slowed, by the use of some medications, or with surgical treatment, at least for a period of time. Oral corticosteroids within 3 mo of diagnosis and early thiopurine use within 1 year were recently shown over several decades to independently affect the likelihood of intestinal surgery[25]. Another long-term study suggested that immunomodulator use for over 6 mo reduced the risk for first surgery, particularly in non-stricturing non-penetrating Crohn's disease[26]. Other long-term studies have independently suggested that the disease may start as an inflammatory process with progressive development over time to more complex disease with stricture and fistula formation[27-29]. Once initiated, it is likely that numerous genetic and environmental factors play a role in regulating the rate of progression, but these are poorly understood. Moreover, the "progression" of the disease itself may not necessarily be a linear process but rather progression may occur in a step-wise fashion with prolonged symptom-free periods over many decades[30].

Crohn's disease may also initially present as an already advanced and clinically complex disease with extensive or multiple jejunoileal strictures[16], sometimes even with free perforation of the small intestine, large intra-abdominal inflammatory masses, and deeply penetrating fistulae (*e.g.*, ileosigmoid fistula). In some, it has been hypothesized that recurrent disease may occur as a patterned clinical response, possibly related to specific genetic regulatory factors. For instance, recurrent stenotic events may result in a localized ileocecal resection, "new" erosions and ulcers in the "neo-terminal" ileum, and further stricture formation, recurrent obstructive symptoms and another resection[31]. Or, in some, recurrent penetrating events with fistula and abscess formation may occur[31].

Recently, additional long-term studies of post-operative Crohn's disease have been reported[32-34]; even here, cigarette smoking has been again identified as the strongest risk factor for recurrence[34]. Clinical experience has also shown that classifying clinical behavior in Crohn's disease is difficult and may not be truly reflective of natural history as the rates of development of a complication, such as a stricture, may differ remarkably, not only between different patients, but even in the same patient. Some may have either a rapidly progressive inflammatory process, or alternatively, a low grade sub-clinical process, possibly present for months, that suddenly becomes clinically expressed. A recent report noted that 10 years following a resection for ileo-cecal disease, only about half were free of clinical recurrence and about 30% needed added surgical treatment[32].

AGE-RELATED PHENOTYPIC EXPRESSION

Early historical studies suggested that the phenotypic clinical expression of Crohn's disease differed substantially, depending on the age of initial diagnosis[35-44]. This age-dependent phenotypic clinical expression probably, in part, reflects an age-dependent regulation of the inflammatory process[40]. Disease developing earlier in children and adolescents tends to be much more severe, often resulting in significant disease complications, including strictures or fistulae, or both[40-45]. It is also more extensive in childhood, often involving multiple sites in the small and large intestine, with a higher frequency of involvement of the upper gastrointestinal tract[40-45]. Comparative studies also show significant differences in clinical expression between children and adults[41,42] as well as the elderly[46,47]. Others have defined a difference in some "immune-reactive" characteristics of early-onset compared to late-onset Crohn's disease[48-50]. A hypothesis that suggests that a dysregulated immune response occurs, likely affected by aging *per se*, and leading to different phenotypic disease expressions of Crohn's disease, needs to be further elucidated.

CLINICOPATHOLOGICAL CORRELATIONS

Clinical and pathological correlations have been explored during the long-term clinical course of Crohn's disease. Some early historical descriptions tended to avoid the pos-

sible temporal sequence of progression of pathological lesions and focused on their prognostic significance[51,52]. However, more recent studies related to this chronological sequence have hypothesized that early small ulcers or granulomas initially develop with ongoing progression to later sinuses and strictures complicating large ulcers[53]. These have also confirmed that this granulomatous inflammation may be a histopathological marker for an early phase of the inflammatory process in Crohn's disease, at least prior to development of fibrotic strictures and fistulous tracts[53]. Granulomatous inflammatory change has been documented in multiple endoscopic biopsies and surgically-resected specimens obtained over many decades from the same patient[29,54]. Often, long intervals of relatively symptom-free disease may be documented[29,54]. This temporal pattern may indicate multiple initiating events in Crohn's disease with different rates of progression, or alternatively, the presence of granulomas may simply reflect ongoing active inflammation, even with subclinical or asymptomatic disease.

These studies also suggested a geographic change in the location of detectable Crohn's disease along the length of the gastrointestinal tract with extended periods of time[29]. For instance, granulomatous ileal involvement was defined many years after initial colonic disease, and gastroduodenal disease occurred after ileocolic resection. If there was a single event that initiated this granulomatous inflammatory process, then different tissues along the length of the gastrointestinal tract may develop a granulomatous response at different rates, or alternatively, there might be multiple or recurring initiating events. Possibly, different gastrointestinal sites may differ in sensitivity to a possible initiating event (or infectious agent). This could be due to a site-specific differential in intestinal permeability or differing immunological responses along the length of the gastrointestinal tract[55,56].

SUMMARY AND FUTURE CONSIDERATIONS

Changes in the clinical features, course and prognosis of inflammatory bowel disease during the last 5 decades has been recently evaluated[57]. In spite of variations in presentation and initial course, the long-term prognosis for Crohn's disease appeared to be stable. A database review for a similar time period noted that about a third of patients had ileitis, colitis or ileocolitis at the time of diagnosis. After about 20 years, half suffered an intestinal complication. Only 10% had a prolonged clinical remission. About a third required steroid therapy to some extent and a third needed surgical treatment after steroids were used. Hospitalization was necessary in 20% and about half needed surgery within 10 years from diagnosis[58]. Further studies to examine the effects of different therapies on the natural history of Crohn's disease are in early stages. A long term evaluation of a population-based inception cohort from Hungary documented a reduction in surgical rates associated with increased and earlier use of azathioprine[59]. Although some consider endoscopic mucosal healing as a useful target in ulcerative colitis, the role on the long-term natural history of Crohn's disease has been more difficult to establish and is not known. Additional information on the effects of biological agents, especially TNF blockers[60], on the long-term natural history is critical. There is evidence that these agents may reduce disease complications requiring surgical treatment, but a significant adverse risk profile remains, particularly for serious opportunistic infections[61]. Some have hypothesized that directing focus to induction of a "deep remission" may have potential to change natural history[62], even if the precise cause of Crohn's disease is not defined. Time will tell.

REFERENCES

1 **Ventham NT**, Kennedy NA, Nimmo ER, Satsangi J. Beyond gene discovery in inflammatory bowel disease: the emerging role of epigenetics. *Gastroenterology* 2013; **145**: 293-308 [PMID: 23751777 DOI: 10.1053/j.gastro.2013.05.050]

2 **Lees CW**, Satsangi J. Genetics of inflammatory bowel disease: implications for disease pathogenesis and natural history. *Expert Rev Gastroenterol Hepatol* 2009; **3**: 513-534 [PMID: 19817673 DOI: 10.1586/egh.09.45]

3 **Henckaerts L**, Van Steen K, Verstreken I, Cleynen I, Franke A, Schreiber S, Rutgeerts P, Vermeire S. Genetic risk profiling and prediction of disease course in Crohn's disease patients. *Clin Gastroenterol Hepatol* 2009; **7**: 972-980.e2 [PMID: 19422935 DOI: 10.1016/j.cgh.2009.05.001]

4 **Beaugerie L**, Sokol H. Clinical, serological and genetic predictors of inflammatory bowel disease course. *World J Gastroenterol* 2012; **18**: 3806-3813 [PMID: 22876031 DOI: 10.3748/wjg.v18.i29.3806]

5 **Xavier RJ**, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007; **448**: 427-434 [PMID: 17653185 DOI: 10.1038/nature06005]

6 **Molodecky NA**, 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; **142**: 46-54.e42; quiz e30 [PMID: 22001864 DOI: 10.1053/j.gastro.2011.10.001]

7 **Williams GT**, Williams WJ. Granulomatous inflammation--a review. *J Clin Pathol* 1983; **36**: 723-733 [PMID: 6345591 DOI: 10.1136/jcp.36.7.723]

8 **Gasche C**, Scholmerich J, Brynskov J, D'Haens G, Hanauer SB, Irvine EJ, Jewell DP, Rachmilewitz D, Sachar DB, Sandborn WJ, Sutherland LR. 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 [PMID: 10701144 DOI: 10.1097/00054725-200002000-00002]

9 **Silverberg MS**, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus EV, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; **19** Suppl A: 5A-36A [PMID: 16151544]

10 **Freeman HJ**. Application of the Vienna Classification for Crohn's disease to a single clinician database of 877 patients. *Can J Gastroenterol* 2001; **15**: 89-93 [PMID: 11240378]

11 **Freeman HJ**. Application of the Montreal classification for Crohn's disease to a single clinician database of 1015 pa-

tients. *Can J Gastroenterol* 2007; **21**: 363-366 [PMID: 17571169]
12 **Nugent FW**, Glaser D, Fernandez-Herlihy L. Crohn's colitis associated with granulomatous bone disease. *N Engl J Med* 1976; **294**: 262-263 [PMID: 1244552 DOI: 10.1056/NEJM197601292940507]
13 **Freeman HJ**, Kwong R, Sacks SL. Granulomatous vaginal ulceration due to metastatic cutaneous Crohn's disease. *Can J Gastroenterol* 1995; **9**: 183-186
14 **Freeman HJ**, Owen D, Millan M. Granulomatous osteonecrosis in Crohn's disease. *Can J Gastroenterol* 2000; **14**: 951-954 [PMID: 11125186]
15 **Freeman HJ**, Maguire J. Sellar inflammatory mass with inflammatory bowel disease. *Can J Gastroenterol* 2010; **24**: 58-60 [PMID: 20186358]
16 **Freeman HJ**. Long-term clinical behavior of jejunoileal involvement in Crohn's disease. *Can J Gastroenterol* 2005; **19**: 575-578 [PMID: 16151550]
17 **Freeman HJ**. Familial Crohn's disease in single or multiple first-degree relatives. *J Clin Gastroenterol* 2002; **35**: 9-13 [PMID: 12080219 DOI: 10.1097/00004836-200207000-00004]
18 **Cuthbert AP**, Fisher SA, Mirza MM, King K, Hampe J, Croucher PJ, Mascheretti S, Sanderson J, Forbes A, Mansfield J, Schreiber S, Lewis CM, Mathew CG. The contribution of NOD2 gene mutations to the risk and site of disease in inflammatory bowel disease. *Gastroenterology* 2002; **122**: 867-874 [PMID: 11910337 DOI: 10.1053/gast.2002.32415]
19 **Newman B**, Silverberg MS, Gu X, Zhang Q, Lazaro A, Steinhart AH, Greenberg GR, Griffiths AM, McLeod RS, Cohen Z, Fernández-Viña M, Amos CI, Siminovitch K. CARD15 and HLA DRB1 alleles influence susceptibility and disease localization in Crohn's disease. *Am J Gastroenterol* 2004; **99**: 306-315 [PMID: 15046222 DOI: 10.1111/j.1572-0241.2004.04038.x]
20 **Chow DK**, Sung JJ, Wu JC, Tsoi KK, Leong RW, Chan FK. Upper gastrointestinal tract phenotype of Crohn's disease is associated with early surgery and further hospitalization. *Inflamm Bowel Dis* 2009; **15**: 551-557 [PMID: 19067420 DOI: 10.1002/ibd.20804]
21 **Odes S**, Vardi H, Friger M, Wolters F, Hoie O, Moum B, Bernklev T, Yona H, Russel M, Munkholm P, Langholz E, Riis L, Politi P, Bondini P, Tsianos E, Katsanos K, Clofent J, Vermeire S, Freitas J, Mouzas I, Limonard C, O'Morain C, Monteiro E, Fornaciari G, Vatn M, Stockbrugger R. Effect of phenotype on health care costs in Crohn's disease: A European study using the Montreal classification. *J Crohns Colitis* 2007; **1**: 87-96 [PMID: 21172190 DOI: 10.1016/j.crohns.2007.08.004]
22 **Cullen G**, Donnellan F, Doherty GA, Smith M, Cheifetz AS. Evaluation of the small bowel in inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol* 2013; **7**: 239-251 [PMID: 23445233 DOI: 10.1586/egh.13.11]
23 **Abreu MT**, Taylor KD, Lin YC, Hang T, Gaiennie J, Landers CJ, Vasiliauskas EA, Kam LY, Rojany M, Papadakis KA, Rotter JI, Targan SR, Yang H. Mutations in NOD2 are associated with fibrostenosing disease in patients with Crohn's disease. *Gastroenterology* 2002; **123**: 679-688 [PMID: 12198692 DOI: 10.1053/gast.2002.35393]
24 **Heliö T**, Halme L, Lappalainen M, Fodstad H, Paavola-Sakki P, Turunen U, Färkkilä M, Krusius T, Kontula K. CARD15/NOD2 gene variants are associated with familially occurring and complicated forms of Crohn's disease. *Gut* 2003; **52**: 558-562 [PMID: 12631669 DOI: 10.1136/gut.52.4.558]
25 **Ramadas AV**, Gunesh S, Thomas GA, Williams GT, Hawthorne AB. Natural history of Crohn's disease in a population-based cohort from Cardiff (1986-2003): a study of changes in medical treatment and surgical resection rates. *Gut* 2010; **59**: 1200-1206 [PMID: 20650924 DOI: 10.1136/gut.2009.202101]
26 **Picco MF**, Zubiaurre I, Adluni M, Cangemi JR, Shelton D. Immunomodulators are associated with a lower risk of first surgery among patients with non-penetrating non-stricturing Crohn's disease. *Am J Gastroenterol* 2009; **104**: 2754-2759 [PMID: 19584832 DOI: 10.1038/ajg.2009.387]
27 **Cosnes J**, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, Gendre JP. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002; **8**: 244-250 [PMID: 12131607 DOI: 10.1097/00054725-200207000-00002]
28 **Louis E**, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001; **49**: 777-782 [PMID: 11709511 DOI: 10.1136/gut.49.6.777]
29 **Freeman HJ**. Natural history and clinical behavior of Crohn's disease extending beyond two decades. *J Clin Gastroenterol* 2003; **37**: 216-219 [PMID: 12960719 DOI: 10.1097/00004836-200309000-00005]
30 **Freeman HJ**. Temporal and geographic evolution of longstanding Crohn's disease over more than 50 years. *Can J Gastroenterol* 2003; **17**: 696-700 [PMID: 14679418]
31 **Greenstein AJ**, Lachman P, Sachar DB, Springhorn J, Heimann T, Janowitz HD, Aufses AH. Perforating and non-perforating indications for repeated operations in Crohn's disease: evidence for two clinical forms. *Gut* 1988; **29**: 588-592 [PMID: 3396946 DOI: 10.1136/gut.29.5.588]
32 **Margagnoni G**, Aratari A, Mangone M, Moretti A, Spagnolo A, Fascì Spurio F, Luchetti R, Papi C. Natural history of ileo-caecal Crohn's disease after surgical resection. A long term study. *Minerva Gastroenterol Dietol* 2011; **57**: 335-344 [PMID: 22105722]
33 **Swoger JM**, Regueiro M. Evaluation for postoperative recurrence of Crohn disease. *Gastroenterol Clin North Am* 2012; **41**: 303-314 [PMID: 22500519 DOI: 10.1016/j.gtc.2012.01.011]
34 **Buisson A**, Chevaux JB, Allen PB, Bommelaer G, Peyrin-Biroulet L. Review article: the natural history of postoperative Crohn's disease recurrence. *Aliment Pharmacol Ther* 2012; **35**: 625-633 [PMID: 22313322 DOI: 10.1111/j.1365-2036.2012.05002.x]
35 **Gryboski JD**, Spiro HM. Prognosis in children with Crohn's disease. *Gastroenterology* 1978; **74**: 807-817 [PMID: 25221]
36 **Harper PC**, McAuliffe TL, Beeken WL. Crohn's disease in the elderly. A statistical comparison with younger patients matched for sex and duration of disease. *Arch Intern Med* 1986; **146**: 753-755 [PMID: 3963958 DOI: 10.1001/archinte.1986.00360160189025]
37 **Farmer RG**, Michener WM. Prognosis of Crohn's disease with onset in childhood or adolescence. *Dig Dis Sci* 1979; **24**: 752-757 [PMID: 487911 DOI: 10.1007/BF01317207]
38 **Polito JM**, Childs B, Mellits ED, Tokayer AZ, Harris ML, Bayless TM. Crohn's disease: influence of age at diagnosis on site and clinical type of disease. *Gastroenterology* 1996; **111**: 580-586 [PMID: 8780560 DOI: 10.1053/gast.1996.v111.pm8780560]
39 **Weinstein TA**, Levine M, Pettei MJ, Gold DM, Kessler BH, Levine JJ. Age and family history at presentation of pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2003; **37**: 609-613 [PMID: 14581806 DOI: 10.1097/00005176-200311000-00020]
40 **Freeman HJ**. Age-dependent phenotypic clinical expression of Crohn's disease. *J Clin Gastroenterol* 2005; **39**: 774-777 [PMID: 16145338 DOI: 10.1097/01.mcg.0000177243.51967.ca]
41 **Freeman HJ**. Comparison of longstanding pediatric-onset and adult-onset Crohn's disease. *J Pediatr Gastroenterol Nutr* 2004; **39**: 183-186 [PMID: 15269625 DOI: 10.1097/00005176-200408000-00011]
42 **Freeman HJ**. Long-term prognosis of early-onset Crohn's disease diagnosed in childhood or adolescence. *Can J Gastroenterol* 2004; **18**: 661-665 [PMID: 15565205]
43 **Vernier-Massouille G**, Balde M, Salleron J, Turck D, Dupas JL, Mouterde O, Merle V, Salomez JL, Branche J, Marti R, Lerebours E, Cortot A, Gower-Rousseau C, Colombel JF. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology* 2008; **135**: 1106-1113 [PMID: 18692056 DOI: 10.1053/j.gastro.2008.06.079]
44 **Abraham BP**, Mehta S, El-Serag HB. Natural history of pediatric-onset inflammatory bowel disease: a systematic review. *J Clin Gastroenterol* 2012; **46**: 581-589 [PMID: 22772738 DOI: 10.1097/MCG.0b013e318247c32f]
45 **Pigneur B**, Seksik P, Viola S, Viala J, Beaugerie L, Girardet JP, Ruemmele FM, Cosnes J. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease.

Inflamm Bowel Dis 2010; **16**: 953-961 [PMID: 19834970 DOI: 10.1002/ibd.21152]
46 **Freeman HJ**. Crohn's disease initially diagnosed after age 60 years. *Age Ageing* 2007; **36**: 587-589 [PMID: 17913760 DOI: 10.1093/ageing/afm106]
47 **Charpentier C**, Salleron J, Savoye G, Fumery M, Merle V, Laberenne JE, Vasseur F, Dupas JL, Cortot A, Dauchet L, Peyrin-Biroulet L, Lerebours E, Colombel JF, Gower-Rousseau C. Natural history of elderly-onset inflammatory bowel disease: a population-based cohort study. *Gut* 2013; Epub ahead of print [PMID: 23408350]
48 **Kugathasan S**, Saubermann LJ, Smith L, Kou D, Itoh J, Binion DG, Levine AD, Blumberg RS, Fiocchi C. Mucosal T-cell immunoregulation varies in early and late inflammatory bowel disease. *Gut* 2007; **56**: 1696-1705 [PMID: 17682002 DOI: 10.1136/gut.2006.116467]
49 **Dubinsky MC**, Kugathasan S, Mei L, Picornell Y, Nebel J, Wrobel I, Quiros A, Silber G, Wahbeh G, Katzir L, Vasiliauskas E, Bahar R, Otley A, Mack D, Evans J, Rosh J, Hemker MO, Leleiko N, Crandall W, Langton C, Landers C, Taylor KD, Targan SR, Rotter JI, Markowitz J, Hyams J. Increased immune reactivity predicts aggressive complicating Crohn's disease in children. *Clin Gastroenterol Hepatol* 2008; **6**: 1105-1111 [PMID: 18619921 DOI: 10.1016/j.cgh.2008.04.032]
50 **Veny M**, Esteller M, Ricart E, Piqué JM, Panés J, Salas A. Late Crohn's disease patients present an increase in peripheral Th17 cells and cytokine production compared with early patients. *Aliment Pharmacol Ther* 2010; **31**: 561-572 [PMID: 19958311 DOI: 10.1111/j.1365-2036.2009.04209.x]
51 **Markowitz J**, Kahn E, Daum F. Prognostic significance of epithelioid granulomas found in rectosigmoid biopsies at the initial presentation of pediatric Crohn's disease. *J Pediatr Gastroenterol Nutr* 1989; **9**: 182-186 [PMID: 2809938 DOI: 10.1097/00005176-198908000-00009]
52 **Gupta N**, Cohen SA, Bostrom AG, Kirschner BS, Baldassano RN, Winter HS, Ferry GD, Smith T, Abramson O, Gold BD, Heyman MB. Risk factors for initial surgery in pediatric patients with Crohn's disease. *Gastroenterology* 2006; **130**: 1069-1077 [PMID: 16618401 DOI: 10.1053/j.gastro.2006.02.003]
53 **Kelly JK**, Sutherland LR. The chronological sequence in the pathology of Crohn's disease. *J Clin Gastroenterol* 1988; **10**: 28-33 [PMID: 3356881 DOI: 10.1097/00004836-198802000-00008]
54 **Freeman HJ**. Granuloma-positive Crohn's disease. *Can J Gastroenterol* 2007; **21**: 583-587 [PMID: 17853953]
55 **Meddings JB**, Gibbons I. Discrimination of site-specific alterations in gastrointestinal permeability in the rat. *Gastroenterology* 1998; **114**: 83-92 [PMID: 9428222 DOI: 10.1016/S0016-5085(98)70636-5]
56 **Camerini V**, Panwala C, Kronenberg M. Regional specialization of the mucosal immune system. Intraepithelial lymphocytes of the large intestine have a different phenotype and function than those of the small intestine. *J Immunol* 1993; **151**: 1765-1776 [PMID: 8345182]
57 **Jess T**, Riis L, Vind I, Winther KV, Borg S, Binder V, Langholz E, Thomsen OØ, Munkholm P. Changes in clinical characteristics, course, and prognosis of inflammatory bowel disease during the last 5 decades: a population-based study from Copenhagen, Denmark. *Inflamm Bowel Dis* 2007; **13**: 481-489 [PMID: 17206705 DOI: 10.1002/ibd.20036]
58 **Peyrin-Biroulet L**, Loftus EV, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010; **105**: 289-297 [PMID: 19861953 DOI: 10.1038/ajg.2009.579]
59 **Lakatos PL**, Golovics PA, David G, Pandur T, Erdelyi Z, Horvath A, Mester G, Balogh M, Szipocs I, Molnar C, Komaromi E, Veres G, Lovasz BD, Szathmari M, Kiss LS, Lakatos L. Has there been a change in the natural history of Crohn's disease? Surgical rates and medical management in a population-based inception cohort from Western Hungary between 1977-2009. *Am J Gastroenterol* 2012; **107**: 579-588 [PMID: 22233693 DOI: 10.1038/ajg.2011.448]
60 **Thomson AB**, Gupta M, Freeman HJ. Use of the tumor necrosis factor-blockers for Crohn's disease. *World J Gastroenterol* 2012; **18**: 4823-4854 [PMID: 23002356 DOI: 10.3748/wjg.v18.i35.4823]
61 **Cerqueira RM**, Lago PM. Clinical factors predictive of Crohn's disease complications and surgery. *Eur J Gastroenterol Hepatol* 2013; **25**: 129-134 [PMID: 23104203 DOI: 10.1097/MEG.0b013e32835a7eed]
62 **Orlando A**, Guglielmi FW, Cottone M, Orlando E, Romano C, Sinagra E. Clinical implications of mucosal healing in the management of patients with inflammatory bowel disease. *Dig Liver Dis* 2013; **45**: 986-991 [PMID: 23993738]

P- Reviewer: Kim SO **S- Editor**: Wen LL
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ISSN 1007-9327
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