Dig Dis Sci (2016) 61:3278–3284
DOI 10.1007/s10620-016-4189-z

ORIGINAL ARTICLE

Diagnostic Delay Is Associated with a Greater Risk of Early Surgery in a French Cohort of Crohn's Disease Patients

Stéphane Nahon[1] · Pierre Lahmek[2] · Thierry Paupard[3] · Bruno Lesgourgues[1] · Stanislas Chaussade[4] · Laurent Peyrin-Biroulet[5] · Vered Abitbol[4]

Received: 14 February 2016 / Accepted: 30 April 2016 / Published online: 20 May 2016

Abstract
Aim To investigate whether a diagnostic delay is associated with a poor outcome in Crohn's disease (CD).
Methods Medical and socioeconomic characteristics as well as medications and need for surgery of consecutive CD adults patients followed in three referral centers were prospectively recorded using an electronic database (Focus_MICI®). A long diagnostic delay was defined by the upper quartile. We compared patients with long diagnostic delay to those with earlier diagnosis regarding the time to: (1) first intestinal surgery, (2) first use of immunosuppressants (IMSs), and (3) first use of anti-tumor necrosis factor (anti-TNF) therapy using the Kaplan–Meier test and the log-rank test.
Results A total of 497 patients with CD (53.6 % women) were analyzed. Median diagnostic delay was 5 months (IQR 25–75 %: 2–13 months). Median follow-up was 9 years (IQR 4–16.2), and 148 (29.8 %) patients had major surgery. There were no significant differences between patients with late and early diagnosis regarding age at diagnosis, disease phenotype, need for IMS therapy, and need for anti-TNF therapy. Time to first major surgery was shorter in patients with late diagnosis ($p = 0.05$).
Conclusion In this large multicenter prospective cohort of French CD patients, a long diagnostic delay (>13 months) increased the risk of early surgery. No associated factors could be identified in this study.

Keywords Crohn's disease · Diagnostic delay · Surgery

Abbreviations

CD	Crohn's disease
anti-TNF	Anti-tumor necrosis factor
IMS	Immusuppressant

Introduction

Crohn's disease (CD) is a chronic disorder of the gastrointestinal tract that can lead to bowel damage overtime. Most patients with CD will eventually develop a structuring or a penetrating complication [1–3]. Increasing evidence suggests that early intensive therapy with immunomodulators and/or biologics is associated with an increased probability of mucosal healing and early-sustained remission without steroids [4–7]. Given the risks of IMS therapies, only patients who would have experienced a disabling and/or severe disease are usually considered for early intensive therapy. However, evolution of CD is variable and difficult to predict on information available at diagnosis. Some patients will experience an aggressive disease with complications, whereas few others will have an indolent disease with only few flare-ups [6].

Electronic supplementary material The online version of this article (doi:10.1007/s10620-016-4189-z) contains supplementary material, which is available to authorized users.

✉ Stéphane Nahon
snahon@ch-montfermeil.fr; snahon@club-internet.fr

[1] Service d'Hépato-Gastroentérologie, Groupe Hospitalier Intercommunal Le Raincy-Montfermeil, 10, avenue du Général Leclerc, 93370 Montfermeil, France

[2] Hôpital Emile Roux, Limeil-Brevannes, France

[3] Division of Gastroenterology and Hepatology, Hôpital de Dunkerque, Dunkirk, France

[4] Division of Gastroenterology and Hepatology, Hopital Cochin, Paris, France

[5] Inserm U954 and Department of Gastroenterology, Lorraine University, Vandoeuvre-les-Nancy, France

Recently, Peyrin-Biroulet et al. [8] proposed a definition of severe CD based on impact of disease on patient, inflammatory burden and disease course, including structural damage. In the Swiss IBD cohort a delay in diagnosis was associated with a pejorative evolution of CD [9]. Whether these data can be extrapolated to other countries has yet to be determined due to differences in healthcare system worldwide. We recently reported our experience on the lack of predictive factors of delayed diagnosis related to disease characteristics and socioeconomic criteria at diagnosis [10]. The aim of this work was to determine whether a diagnostic delay was associated with a poor outcome in CD using a prospective cohort of French adult patients.

Patients and Methods

All consecutive CD adult patients followed in three referral centers [Groupe Hospitalier Le Raincy-Montfermeil (suburb of Paris), Hôpital Cochin (Paris), and Centre Hospitalier de Dunkerque (north of France)] were invited to participate in a prospective cohort study (Focus_MICI®). All the participants in the study gave informed consent. The cohort was declared to the French Commission on Information Technology and Liberties (CNIL) by the three centers. Clinical and socioeconomic characteristics as well as disease outcomes (need for immunosuppressive therapy and surgery) of all consecutive CD patients between September 2002 and July 2014 were recorded using a prospectively maintained electronic database (FileMaker Pro V 12.0).

Definition of Diagnostic Delay

Diagnostic delay was defined as the time period (months) from the first symptom onset to establishment of CD diagnosis by the gastroenterologist. All consecutive patients diagnosed in our hospitals were asked about their symptom onset, and their diagnostic delay was recorded at diagnosis. In patients with CD diagnosis made outside our centers, diagnostic delay was calculated through patient's interview and by reviewing medical charts of patients. Patients who failed to provide exact date of diagnosis were excluded from the study.

Similarly to Vavrika et al. [11] we defined "a long diagnostic delay" as the upper quartile.

Data Collected

The following sociodemographic and characteristics of CD data were collected: age, gender, marital, education and employment status, family history of IBD, symptoms at diagnosis (and the most relevant of them), extraintestinal manifestation (peripheral arthritis, ankylosing spondylitis, aphthous stomatitis, uveitis, erythema nodosa, pyoderma gangrenosum), disease location, and phenotype according to Montreal classification and anoperineal lesions.

We also collected birth country (France, Europe, North Africa, and others), as well as language understanding (poor vs. good, according to the quality of the rephrasing by the patient) assessed by gastroenterologists (SN, VA, TP).

For each medication [5-ASA, budesonide, corticosteroids, purine antimetabolites and methotrexate, anti-TNF (infliximab, adalimumab)] the following data were recorded: dates of start and end of treatment (or last news when ongoing medication at last clinical visit).

Main Outcomes

The following indicators of a poor outcome were considered: time to first major intestinal surgery, time to introduction of an IMS, and time to first use of an anti-TNF agent from disease diagnosis. The following intestinal surgery procedures were considered as major surgery: stricturoplasty, ileal resection, ileocecal resection, small bowel resection other than terminal ileum, partial colectomy, subtotal colectomy (rectum left in situ), proctocolectomy, ileostomy, and colostomy). Perianal surgical procedures for treatment of perianal fistulas and/or abscesses were also collected.

Statistical Analysis

Analyses were conducted with long diagnosis delay as the primary dependent variable. Variables were coded both categorically and continuously. Data were expressed as mean ± SD or as median and interquartile range.

Univariate analysis was performed to compare patients with diagnostic delay to those with earlier diagnosis regarding the rates of: (1) the first major intestinal surgery (excluding anoperineal surgery), (2) IMS therapies, and (3) anti-TNF therapies.

For these analyses, we used Student's t test and ANOVA for continuous data and the Chi-square test or Fisher's exact test for categorical data. Significant variables resulting from univariate analyses ($p \leq 0.20$) were processed in a stepwise multivariate model. Individual odds ratio (OR) and their 95 % confidence intervals (CIs) were computed for each variable.

Time to: (1) first surgery, (2) first anti-TNF therapy use, and (3) first IMS use was analyzed using the Kaplan–Meier and groups were compared with the log-rank method.

A two-tailed p value of <0.05 was considered statistically significant. Statistical analysis was performed by SPSS software (version 18.0).

Results

Demographics and Clinical Characteristics

Data of 519 patients with CD were recorded in the database. The diagnostic delay could not be calculated in 22 patients who were excluded from the study. A total of 497 patients with CD (53.6 % women) were analyzed. The characteristics of the studied cohort are presented in Table 1. Median age at diagnosis was 25.6 years (IQR 25–75: 19.4–35.2). Four hundred and ten (82.4 %) patients were diagnosed at age ≤40 years. Median follow-up was 9 years (IQR 25–75: 4–16.2). One hundred and thirty-eight (28.3 %) patients were active smokers and 109 (22.4 %) former smokers. CD location, at time of diagnosis, according to the Montreal classification was: 196 (41.1 %) L1, 121 (25.4 %) L2, and 154 (32.3 %) L3. CD behavior, at the end of observation time, according to Montreal classification was: 272 (58.1 %) B1, 143 (30.6 %) B2, and 53 (11.3 %) B3. One hundred and seven (21.5 %) patients had a family history (first- or second-degree) of inflammatory bowel disease.

Table 1 Clinical characteristics of the population

Characteristics (n)[a]	n (%)
Gender (497)	
Male	232 (46.7 %)
Female	265 (53.3 %)
Median age at diagnosis (years)	25.6 (IQR 25–75 %: 19.4–35.2)
Age at diagnosis (years)	
<40	409 (82.3 %)
≥40	88 (17.7 %)
Median diagnostic delay (months)	5 (IQR 25–75 %: 2–13)
Late diagnosis (>13 months)	122 (25 %)
Median of follow-up (years)	9 (IQR 25–75 %: 4–16.2)
Active smoker (487)	138 (28.3 %)
Former smoker (487)	109 (22.4 %)
Non-smoker	240 (49.3 %)
CD location (477)	
L1	196 (41.1 %)
L2	121 (25.4 %)
L3	154 (32.3 %)
L4	5 (1 %)
CD behavior (468)	
B1	272 (58.1 %)
B2	143 (30.6 %)
B3	53 (11.3 %)

[a] Number of patients with available data

Prior and Ongoing Medications (Table 2)

One hundred and sixty-one (37.1 %) patients had ongoing thiopurines treatment, while 132 (30.4 %) had previous exposure; 28 (6.5 %) had ongoing methotrexate treatment, while 50 (11.7 %) were previously exposed to this drug; 87 (20.2 %) had ongoing infliximab treatment, while 69 (16 %) had prior exposure, and 118 (27.3 %) had ongoing adalimumab treatment, while 48 (11.1 %) were previously exposed to this anti-TNF agent.

Surgery (Table 3)

One hundred and forty-eight (29.8 %) patients had a major surgery and 73 (14.7 %) a perianal surgery during follow-up, and 21 (4.2 %) had both major surgery and perianal surgery.

The surgical procedures were as follows (some patients may have had multiple resections): ileal resection ($N = 21$), ileocecal resection ($N = 117$), colectomy ($N = 27$), definitive ileostomy ($N = 4$), jejunal resection ($N = 2$), colostomy ($N = 1$), and stricturoplasty ($N = 3$). Mean number of intestinal resection was 1.5 ± 0.9.

Diagnostic Delay

Median diagnostic delay was 5 months. Early diagnosis (first quartile) corresponds to a period <2 months from first symptoms to CD diagnosis ($n = 122$ patients), and a late diagnosis corresponds to a period >13 months from first symptoms to CD diagnosis ($n = 122$ patients).

Comparison Between Delayed and Early Diagnosis (Table 4)

Median duration of follow-up did not differ between the two groups (8.8 vs. 9.3 years). There were no significant differences between patients with delayed and earlier diagnosis, at the time of diagnosis, regarding (Table 4): age at diagnosis, disease location (L1, L2, L3), and behavior (B1, B2, B3, B2 + B3) of the disease, use of IMS ($p = 0.6$) or anti-TNF ($p = 0.7$), and median time from diagnosis to the first prescription of IMS or to the first anti-

Table 2 Medication history of the population

Medical treatment (n)[a]	Ongoing	Prior
Thiopurines ($n = 434$)	161 (37.1 %)	132 (30.4 %)
Methotrexate ($n = 431$)	28 (6.5 %)	50 (11.7 %)
Infliximab ($n = 431$)	87 (20.2 %)	69 (16 %)
Adalimumab ($n = 432$)	118 (27.3 %)	48 (11.1 %)

Table 3 Surgery history of the population

	N (%)
Total of patients	497
Patients undergoing intestinal surgery	148 (29.8 %)
Patients undergoing anoperineal surgery	73 (14.7 %)
Patients undergoing both intestinal and anoperineal surgery	21 (4.2 %)
Total of intestinal surgery	175
Ileal resection	21 (12 %)
Ileocecal resection	117 (66.8 %)
Colectomy (partial $n = 10$; subtotal $n = 17$)	27 (15.4 %)
Definitive ileostomy; definitive colostomy	4; 1 (3 %)
Jejunal resections	2 (1 %)
Stricturoplasty (patients may have had multiple resections)	3 (2 %)

Table 4 Comparison of clinical outcome in the two groups (late and earlier diagnosis) by univariate analysis

Characteristics	Late diagnosis	Earlier diagnosis	Odds ratio	IC 95 %	*p*
n	122	375			0.66
Age at diagnosis <40 years	102 (75 %)	307 (75.1 %)	1.13	0.65–1.95	0.7
Sex ratio	51 (41.8 %)	178 (47.8 %)	0.78	0.52–1.18	0.25
Active smokers	33 (26.8 %)	105 (28.8 %)	0.9	0.57–1.43	0.7
Past smokers	31 (25.2 %)	78 (21.4 %)	1.28	0.79–2.06	0.3
Location ($n = 477$)					
L1	54 (45.4 %)	142 (39.7 %)	1.26	0.83–1.92	0.3
L2	24 (20.2 %)	97 (27.1 %)	0.68	0.41–1.13	0.1
L3	39 (32.8 %)	115 (32.1 %)	1.03	0.66–1.6	0.9
Phenotype ($n = 468$)					
B1	62 (53.9 %)	210 (59.5 %)	0.8	0.52–1.22	0.3
B2	37 (32.2 %)	106 (30.0 %)	1.11	0.7–1.74	0.65
B3	16 (13.9 %)	37 (10.5 %)	1.38	0.74–2.59	0.3
B2 + B3	53 (46.1 %)	143 (40.5 %)	1.26	0.82–1.92	0.3
Number of intestinal surgery	41 (33.6 %)	107 (28.5 %)	1.27	0.82–1.99	0.28
Number of perianal surgery	21 (17.2 %)	52 (13.9 %)	1.29	0.74–2.25	0.36
Number of patients treated by IMS (thioguanines or methotrexate)	85 (69.7 %)	246 (65.6 %)	1.12	0.74–1.74	0.6
Number of patients treated by anti-TNF (adalimumab or infliximab)	64 (52.4 %)	178 (47.4 %)	1.22	0.81–1.84	0.34

IMS immunosuppressant

TNF prescription. Median survival time to first major surgery was higher among patients with a long diagnostic delay ($p = 0.05$) (Fig. 1), while median time to first prescription of IMS and anti-TNF therapy did not differ between the two groups (supplementary figure 2 and figure 3).

Discussion

In this French cohort of IBD patients coming from three different and representative referral centers using the same database (Focus_MICI®), we observed that diagnostic delay is associated with an early need for intestinal surgery. Our results are in accordance with those observed in the Swiss IBD cohort and more recently in a cohort of Chinese patients, showing that diagnostic delay is associated with a poor outcome of CD with especially a higher risk of surgery [9, 12, 13]. The median time to diagnosis was quite shorter in our study compared with that observed in the Swiss or Chinese cohort (Table 5). Our findings are in accordance with the French population-based cohort EPIMAD, which records all incident cases of IBD since 1988 in northern France [14]. We can explain the much shorter delay as easy access to health care in France. Indeed, we have previously observed that socioeconomic deprivation does not influence the severity of CD and does not delay time to diagnosis [10, 15]. Our population is similar to the

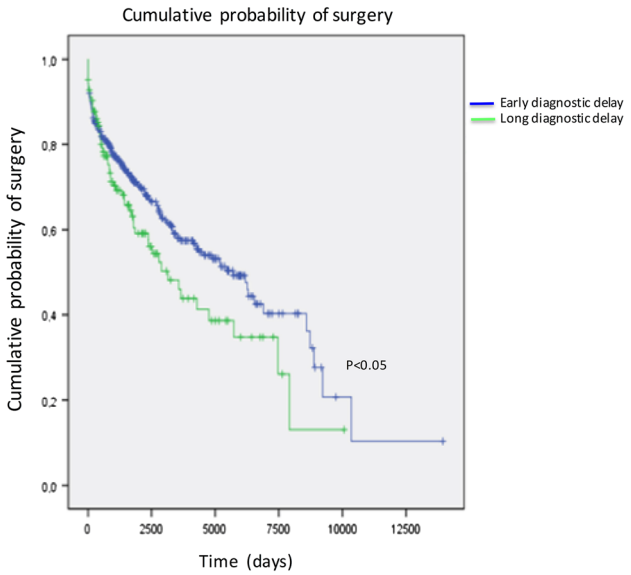

Fig. 1 Median survival time to first major surgery

Swiss IBD cohort at diagnosis in terms of sex ratio, median age at diagnosis, age at diagnosis <40, colonic location, but ileal location was more frequent in our population and ileocolonic location in the Swiss cohort [9]. Conversely, our population differs from the Chinese population in terms of sex ratio, age at diagnosis, and smoker status [13]. In the IBD Swiss cohort, long diagnostic delay was also associated with an increased risk for bowel stenosis, internal fistulas, perianal fistulas, and CD-related intestinal surgery [9]. In our work, despite similar rates of treatments with anti-TNF or IMS, surgery rate was higher in the group of patients with delayed diagnosis. Presumably, diagnosis delay could cause irreversible lesions and disability where medical treatment is less effective because the disease is already advanced or complicated. Because of a lack of clear prognostic factors, optimal therapeutic medical strategies are still missing. In a recent study by the GETAID [2], administration of azathioprine within 6 months of diagnosis of CD was not more effective than conventional management in increasing time of clinical remission. Moreover, the cumulative proportion of patients free of intestinal surgery and anti-TNF therapy did not differ between the two groups [2]. D'Haens et al. [16] showed that early combined immunosuppression (combotherapy) "top-down strategy" is more effective than conventional management "step-up strategy" for induction of remission and reduction of steroid use in patients with recently diagnosed with Crohn's disease (CD). The authors recently evaluated the long-term effects of the "top-down" strategy (induction IFX and maintenance azathioprine (AZA) vs. conventional "step-up" treatment [17]: Top-down treatment resulted in a reduction of flares and a longer flare-free survival compared to step-up treatment in newly diagnosed CD. However, "top-down" strategy did not change rates of remission, surgery, hospitalization, or endoscopic disease activity [17]. Some patients experience a severe disease with poor evolution, whereas others have indolent disease with only few flare-ups [6]. Thus, not all the patients require an aggressive management at diagnosis.

So the determination of strong predictive factors of poor evolution is a real challenge, since they could help to identify patients who might benefit from early introduction of IMS or biologics. Several studies have focused on this issue. Factors identified at diagnosis by these studies were: young age (<40 years), extensive disease, initial need of treatment with steroids, or anoperineal disease at diagnosis [18, 19]. However, these same factors seem to be insufficient to predict disabling disease and poor outcome, as shown by Cosnes and al. [2]. Therefore, other criteria are strongly needed to identify patients with aggressive disease and poor evolution. As the Swiss cohort and the Chinese study [9, 13], our results show that a diagnostic delay is associated with a poor outcome and an increased risk for bowel stenosis, internal fistulas, and CD-related intestinal surgery [9, 13]. So diagnostic delay should be considered as a good and reliable predictive factor of pejorative evolution at diagnosis.

We recently published our experience on the lack of predictive factors of delayed diagnosis related to disease characteristics and socioeconomic criteria at diagnosis [10]. We did not observe any particular difference in the rate of surgery at diagnosis as we might have suspected. However, after a median follow-up of 9 years, the time between diagnosis and the first major surgery was shorter in patients with a delayed diagnostic. We have also

Table 5 Summarizing and comparing diagnostic delay across countries

	Switzerland	China	France
Author	Schoepfer et al. [9]	Li et al. [13]	Nahon et al.
Type of study	National cohort study	Single-center study	Multicentric cohort study
Median time to diagnosis (IQR 25–75) in months	9 (3–24)	10 (2–34)	5 (2–13)

observed that among patients those with later diagnosis had a tendency to have a greater use of anti-TNF therapy and, although these values were not statistically different. Identification of symptoms or signs of early diagnosis remains a clinical challenge. Recently, Danese et al. [20] have conducted a study to identify clinical predictors of early diagnosis of CD. For this purpose, 12 CD specialists identified "Red Flags" signs or symptoms suggestive of CD. A 21-item questionnaire was administered to 36 healthy subjects, 80 patients with irritable bowel syndrome (non-CD group), and 85 patients with recently diagnosed (<18 months) CD. The multivariate analysis identified eight items independently associated with a diagnosis of CD. A wide diffusion of these "Red Flags" to general practitioner could help to reduce the time from symptoms to diagnosis.

The strength of this study is the multicenter and prospective collection of multiple data of CD at diagnosis and prospectively at each visit. We also used the same electronic database (Focus_MICI®) in three hospitals draining different and representative, French CD patients.

One of the main limitations of the study is the possible recall bias of symptoms onset in patients with long history of symptoms before diagnosis or with CD diagnosis made outside our three hospitals.

Conclusion

In this French prospective and multicentric cohort of CD patients, diagnostic delay (>13 months) is associated with earlier major surgery independently of the location and the phenotype of the disease. Long diagnostic delay for CD patients should be now considered as a predictive factor of severe disease and could have an impact to determine better therapeutic strategies. We now know that CD history and prognosis for each patient begins before diagnosis and that shorten diagnostic delay is a new goal.

Compliance with ethical standards

Conflict of interest Stéphane Nahon reports lecturer or advisory board fees from AbbVie, MSD, Vifor Pharma, and Ferring all outside the submitted work. Pierre Lahmek has nothing to disclose. Thierry Paupard reports lecturer or advisory board fees from AbbVie, MSD, Gilead, and Janssen all outside the submitted work. Stanislas Chaussade reports lecturer or advisory board fees from Mayoli, Fujifilm, Given Imaging, MauneaKea. Laurent Peyrin-Biroulet reports consulting fees from Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Therakos, Pharmacosmos, Pilège, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, Pfizer, HAC-Pharma, Index Pharmaceuticals. Lecture fees from Merck, Abbvie, Takeda, Janssen, Takeda, Ferring, Norgine, Tillots, Vifor, Therakos, Mitsubishi, HAC-Pharma. Vered Abitbol reports lecturer or advisory board fees from AbbVie, MSD, Vifor Pharma, and Ferring all outside the submitted work.

Author contributions Stéphane Nahon contributed to study concept and design; Stéphane Nahon, Thierry Paupard, and Vered Abitbol contributed to acquisition of data; Stéphane Nahon, Pierre Lahmek, and Vered Abitbol analyzed and interpreted the data; Stéphane Nahon drafted the manuscript; Bruno Lesgourgues, Thierry Paupard, Stanislas Chaussade, Laurent Peyrin-Biroulet, and Vered Abitbol contributed to critical revision of the manuscript for important intellectual content; Pierre Lahmek performed statistical analysis; Bruno Lesgourgues contributed to technical or material support; Stéphane Nahon and Vered Abitbol supervised the study.

References

1. Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis*. 2002;8:244–250.
2. Cosnes J, Bourrier A, Laharie D, et al. Early administration of azathioprine vs conventional management of Crohn's disease: a randomized controlled trial. *Gastroenterology*. 2013;145:758–765.
3. Thia KT, Sandborn WJ, Harmsen WS, et al. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology*. 2010;139:1147–1155.
4. Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis*. 2010;4:28–62.
5. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362:1383–1395.
6. Peyrin-Biroulet L, Billioud V, D'Haens G, et al. Development of the Paris definition of early Crohn's disease for disease-modification trials: results of an international expert opinion process. *Am J Gastroenterol*. 2012;107:1770–1776.
7. Danese S, Fiorino G, Fernandes C, et al. Catching the therapeutic window of opportunity in early Crohn's disease. *Curr Drug Targets*. 2014;15:1056–1063.
8. Peyrin-Biroulet L, Panes J, Sandborn WJ, et al. Defining disease severity in inflammatory bowel diseases: current and future directions. *Clin Gastroenterol Hepatol*. 2016;14:348–354.
9. Schoepfer AM, Dehlavi MA, Fournier N, et al. Diagnostic delay in Crohn's disease is associated with a complicated disease course and increased operation rate. *Am J Gastroenterol*. 2013;108:1744–1753. (**quiz 1754**).
10. Nahon S, Lahmek P, Lesgourgues B, et al. Diagnostic delay in a French cohort of Crohn's disease patients. *J Crohns Colitis*. 2014;8:964–969.
11. Vavricka SR, Spigaglia SM, Rogler G, et al. Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. *Inflamm Bowel Dis*. 2012;18:496–505.
12. Romberg-Camps MJ, Hesselink-van de Kruijs MA, Schouten LJ, et al. Inflammatory Bowel Disease in South Limburg (the Netherlands) 1991–2002: Incidence, diagnostic delay, and seasonal variations in onset of symptoms. *J Crohns Colitis*. 2009;3:115–124.
13. Li Y, Ren J, Wang G, et al. Diagnostic delay in Crohn's disease is associated with increased rate of abdominal surgery: a retrospective study in Chinese patients. *Dig Liver Dis*. 2015;47:544–548.

14. Chouraki V, Savoye G, Dauchet L, et al. The changing pattern of Crohn's disease incidence in northern France: a continuing increase in the 10- to 19-year-old age bracket (1988–2007). *Aliment Pharmacol Ther*. 2011;33:1133–1142.
15. Nahon S, Lahmek P, Macaigne G, et al. Socioeconomic deprivation does not influence the severity of Crohn's disease: results of a prospective multicenter study. *Inflamm Bowel Dis*. 2009;15:594–598.
16. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet*. 2008;371:660–667.
17. Hoekman D, Baert F, Caenepeel P, et al. Long-term outcomes of top-down versus step-up treatment in newly diagnosed Crohn's disease. *Gastroenterology*. 2015;148:S176.
18. Beaugerie L, Seksik P, Nion-Larmurier I, et al. Predictors of Crohn's disease. *Gastroenterology*. 2006;130:650–656.
19. Louis E, Michel V, Hugot JP, et al. Early development of structuring or penetrating pattern in Crohn's disease is influenced by disease location, number of flares, and smoking but not by NOD2/CARD15 genotype. *Gut*. 2003;52:552–557.
20. Danese S, Fiorino G, Mary JY, et al. Development of red flags index for early referral of adults with symptoms and signs suggestive of Crohn's disease: an IOIBD initiative. *J Crohns Colitis*. 2015;9:601–606.