Crohn's Disease: The First Visit

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Abstract: A Crohn's disease patient's first visit to a new practice is the optimal time to collect important clinical data and identify appropriate therapies. A methodologic approach to this visit is crucial. The focus of this visit should be on preparing the patient for the initiation of treatment, with particular attention to the necessary steps prior to the use of immunosuppressive and biologic agents. This paper is intended to provide recommendations and a checklist for the initial assessment and evaluation of patients with Crohn's disease.

A Crohn's disease patient's first visit to a new practice is a challenging experience for both the patient and gastroenterologist. Often, the patient is accompanied by little clinical data, making the disease course and chronology unclear. The patient may have undergone numerous tests, treatment regimens, hospitalizations, and surgical procedures by previous providers. The patient may be in remission while on therapy, or he or she may have active disease and need a change in treatment. Gastroenterologists can optimize care in new patients by promptly and efficiently confirming the diagnosis, assessing disease activity, and determining the need for a change in treatment. This paper will offer recommendations to optimize a patient's first visit and provide a checklist to improve efficiency (Table 1).

Step One: Obtain Historical Information

The chronology and manifestations of a patient's Crohn's disease may yield insight on future disease course. For example, young age at disease onset (<40 years) may be a predictor of poor prognosis or aggressive disease course, and it may be a factor in determining the need for biologic therapy (Table 2). Other historical predictors of poor prognosis include cigarette smoking, steroid use, disabling symptoms lasting more than 12 months, hospitalizations, weight loss, and the need for surgical resection. It is also important to know a patient's history of extraintestinal manifestations associated with chronic inflammatory bowel disease (IBD)—such as sacroiliitis, ankylosing spondylitis, pyoderma gangrenosum, or uveitis—in order to understand the disease course and choose optimal therapy. Knowing a patient's social and work histories, as well as the disease's

Table 1. Crohn's Disease First Visit Checklist

- ✔ **Obtain historical information:**
  Age of disease onset, family history of IBD, location of disease, previous treatment regimens and surgeries, history of smoking, number of pregnancies, presence and type of extraintestinal manifestations, history of hospitalizations, work history, and quality of life
- ✔ **Evaluate disease activity:**
  CDAI*, Harvey-Bradshaw Index, the original or short-form IBDQ, CBC, CRP, ESR, fecal calprotectin or lactoferrin, endoscopic imaging, and/or radiologic imaging
- ✔ **Consider assessing IBD serology in select patients:**
  pANCA, ASCA, OmpC, *NOD2*, I2, or CBir1
- ✔ **Obtain the patient's vaccination history, and administer appropriate vaccinations:**
  - Check the patient's immunity to MMR, varicella, hepatitis A virus, and hepatitis B virus.
  - Administer vaccines for Tdap, HPV (in females 12–26 years of age), influenza, pneumococcus (in select patients), meningococcus (in select patients, such as college students), hepatitis A virus, and hepatitis B virus.
  - If there are no plans to administer immunosuppressive therapy within 4–12 weeks and the vaccine is indicated based on patient age and/or lack of immunity, live vaccines can be given for MMR, varicella, and herpes zoster (patients ≥60 years of age).
- ✔ **Prepare for therapy:**
  - Measure thiopurine methyltransferase levels (in patients initiating 6-MP or AZA treatment), vitamin B12, vitamin D, CBC, and serum chemistries.
  - Perform chest radiograph and PPD test.
  - Consider a bone density study.

*A CDAI calculator is available at http://www.ibdjohn.com/cdai/.

6-MP=6-mercaptopurine; ASCA=antibodies against *Saccharomyces cerevisiae*; AZA=azathioprine; CBC=complete blood count; CBir1=anti-CBir1 flagellin; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; HPV=human papillomavirus; I2=Crohn's disease–related bacterial sequence; IBD=inflammatory bowel disease; IBDQ=Inflammatory Bowel Disease Questionnaire; MMR=measles, mumps, rubella; NOD2=nucleotide oligomerization domain 2; OmpC=outer membrane porin protein C; pANCA=perinuclear antineutrophil cytoplasmic antibody; PPD=purified protein derivative; Tdap=tetanus, diphtheria, pertussis.

Table 2. When to Consider Biologic Agents

- **Treatment failure:**
  Failure has been described as persistent disease activity measured by an indirect index or direct examination of mucosa, despite adequate dosing of a traditional therapy (including systemic steroids or an immunosuppressive medication). Hospitalization or the need for surgery has also been defined as a treatment failure.
- **Disease burden and location:**
  Gastroduodenal, anorectal, extensive small-bowel disease, fistulas, isolated small-bowel disease, or deep ulcerations on colonoscopy or capsule endoscopy. Extraintestinal disease includes ankylosing spondylitis, pyoderma gangrenosum, and uveitis.
- **Predictors of poor prognosis:**
  Age at disease onset <40 years, history of smoking, extraintestinal manifestations, multiple positive serologies, the need for steroid treatment, >12 months of disabling symptoms, hospitalizations, weight loss, prior resection, high ESR, and/or high CRP levels.

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate.

impact on quality of life, can yield important insight into disease severity and enhance care. Another factor that determines the choice of therapy is disease extent and location. Patients with gastroduodenal, anorectal, perineal, or exclusive small-bowel Crohn's disease may benefit from early use of biologic therapy.[1,2] Early consideration of biologics is also important for patients with extensive small-bowel disease, fistulous disease, and deep ulcerations on endoscopy. A family history of IBD should be obtained, and the disease course and severity should be noted in all affected relatives. A patient's initial history should also include any prior interventions, whether successful or unsuccessful. A meticulous review of these historical data, in addition to imaging and pathology results, may help to confirm a diagnosis of Crohn's disease and enable better understanding of the disease course.

Step Two: Evaluate Disease Activity

If a patient's history and previous evaluation suggest Crohn's disease, a treatment plan should be determined based on objective evidence of disease activity as well as the severity and extent of disease. For example, a patient with a 20-year history of short-segment ileal disease should be managed differently from a patient with newly diagnosed, extensive, colonic Crohn's disease with perineal fistula. Symptoms, laboratory tests (including measurement of inflammatory markers), serologies, and imaging studies can all help to assess disease activity; however, no single gold-standard indicator has been established.[1]

Symptoms

The characteristics and intensity of abdominal pain, as well as the presence of chronic or nocturnal diarrhea, fever, weight loss, and rectal bleeding, may reflect

Table 3. Crohn's Disease Activity Index (CDAI)

Clinical or laboratory variable	Weighting factor
Number of liquid or soft stools each day for 7 days	× 2
Abdominal pain (graded from 0 to 3 based on severity) each day for 7 days	× 5
General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days	× 7
Complications*	× 20
Use of diphenoxylate or opiates for diarrhea	× 30
An abdominal mass (0 for none; 2 for questionable; 5 for definite)	× 10
Absolute deviation of hematocrit from 47% in men and 42% in women	× 6
Percentage deviation from standard weight	× 1

*One point is added for each set of complications: arthralgia or frank arthritis; inflammation of the iris or uveitis; erythema nodosum, pyoderma gangrenosum, or aphthous ulcers; anal fissures, fistulas, or abscesses; other fistulas; and fever (>100 °F) during the previous week.

Remission: CDAI score <150 points.
Moderate-to-severe disease: CDAI score 230–400 points.

Modified from Best WR, et al.[4]

Table 4. Harvey-Bradshaw Index (HBI)

— **General well being**
(0=very well; 1=slightly below average; 2=poor; 3=very poor; 4=terrible)

— **Abdominal pain**
(0=none; 1=mild; 2=moderate; 3=severe)

— **Number of liquid stools per day**
(0=0–1 stools; 1=2–3 stools; 2=4–5 stools; 3=6–7 stools; 4=8–9 stools; 5=10+ stools)

— **Abdominal mass**
(0=none; 1=dubious; 2=definite; 3=tender)

— **Complications**
Arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissures, new fistulas, abscesses (1 point for each)

— **Total score**

Remission: HBI score <3 points.
Relapse: HBI score >7 points.

Modified from Vermeire S, et al.[5]

inflammation.[1,3] It is crucial to use objective measurements to assess inflammation, as patients with irritable bowel syndrome may also have severe pain and diarrhea. Clinical signs include cachexia, abdominal masses, fistulas, or abscesses. Patients should be questioned regarding signs and symptoms of extraintestinal manifestations of IBD, including arthralgias, cutaneous involvement, and ocular problems. In children, anemia, fever, and growth failure with delayed attainment of developmental milestones may be seen. Clinical patterns may imply disease location and type (fibrostenotic, inflammatory, or fistulizing) and may predict outcomes.

Indices

The Crohn's Disease Activity Index (CDAI; Table 3), Harvey-Bradshaw Index (HBI; Table 4), and various endoscopic mucosal assessment scores (Table 5) have been used in clinical studies to determine disease activity and severity as well as response to therapy.[4-8] The short-form Inflammatory Bowel Disease Questionnaire (IBDQ; Table 6) is composed of 10 questions (compared to 32 questions in the original IBDQ), is easily administered, and can be used to follow the disease's impact on quality of life.[8,9] Both the HBI and short-form IBDQ are well suited for use in clinical practice.

The CDAI and HBI have been used in studies to define response and remission.[3,4] However, the CDAI is cumbersome and requires logarithmic regression analysis for calculation. An online CDAI calculator (available at http://www.ibdjohn.com/cdai/) allows for rapid calculation of the index and, thus, is practical for obtaining objective assessments of disease activity over multiple visits. Because the CDAI requires a hemoglobin test, the patient's CDAI score is often unavailable when the patient is being seen in the physician's office. In clinical practice, the HBI score utilizes readily available clinical data and is helpful for defining active disease. Endoscopic indices can be used to quantify ileocolonic lesions and confirm mucosal healing.[6,7]

Biochemical Markers

C-reactive protein (CRP) appears to be an accurate marker of Crohn's disease activity.[10] CRP is an acute-phase protein that is sensitive for detecting inflammation, infection, and tissue injury. In Crohn's disease, CRP level is increased in most patients with active disease and may correlate with CDAI score. A low CRP level may be useful to predict inactive Crohn's disease, whereas a very high CRP level may predict progression to fibrostenotic disease. It should be noted, however, that up to 50% of patients with Crohn's disease will not have an elevated CRP level, despite documented active inflammation.

Fecal calprotectin and lactoferrin are markers of inflammation that correlate with endoscopic disease activity. Schoepfer and colleagues showed that calprotectin correlated most closely with an endoscopic score

Table 5. Simple Endoscopic Score for Crohn's Disease

	Simple endoscopic score			
Variable	**0**	**1**	**2**	**3**
Size of ulcers	None	Aphthous ulcers	Large ulcers	Very large ulcers
Diameter of ulcers	None	0.1–0.5 cm	0.5–2 cm	>2 cm
Ulcerated surface	None	<10%	10–30%	>30%
Affected surface	Unaffected segment	<50%	50–75%	>75%
Narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Modified from Daperno M, et al.[6]

Table 6. Short Inflammatory Bowel Disease Questionnaire

1. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks?
2. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem?
3. How much difficulty have you had, as a result of your bowel problem, doing leisure or sports activities you would have liked to have done over the last 2 weeks?
4. How often during the last 2 weeks have you been troubled by pain in the abdomen?
5. How often during the last 2 weeks have you felt depressed or discouraged?
6. Overall, in the last 2 weeks, how much of a problem have you had passing large amounts of gas?
7. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be?
8. How often during the last 2 weeks have you felt relaxed and free of tension?
9. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the toilet even though your bowels were empty?
10. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem?

Modified from Jowett SL, et al.[9]

of active Crohn's disease when compared to CRP, white blood cell count, and CDAI score.[11] In this study, calprotectin was the only marker that readily discriminated inactive disease from mild, moderate, and severe disease. Since endoscopic visualization has the disadvantages of discomfort and expense, confirmation of markers such as fecal calprotectin or lactoferrin is promising, as these tests offer the possibility for less invasive monitoring of mucosal disease activity.[11] Other fecal markers, such as elastase or S-100 proteins, are under study. Nonetheless, ileocolonoscopy currently remains the gold standard for assessment of intestinal inflammation.

Step Three: Consider Assessing Inflammatory Bowel Disease Serology in Select Patients

A variety of markers and antimicrobial peptides and antibodies have been associated with IBD. They can be used to help distinguish ulcerative colitis from Crohn's disease and to predict prognosis.[12,13] None of these markers are sensitive enough to establish a diagnosis of IBD by themselves. Antibodies against *Saccharomyces cerevisiae* (ASCA) are the most thoroughly studied markers and have a sensitivity of 60% for Crohn's disease. Perinuclear antineutrophil cytoplasmic antibodies (pANCA) have a sensitivity of 40–60% for ulcerative colitis. Outer membrane porin protein C (OmpC) to *Escherichia coli* has a sensitivity of 20–40% for Crohn's disease. These antibodies, as well as a number of other antibodies directed against bacteria, yeasts, or sugars, may have prognostic implications. The nucleotide-binding oligomerization domain 2 (*NOD2*) gene has been associated with fibrostenosing Crohn's disease. Oligomannan (ASCA) has been associated with aggressive disease and the need for surgery. Anti-OmpC has been associated with fibrostenosis, perforating disease, and the need for small-bowel surgery. Crohn's disease–related bacterial sequence (I2) is associated with small-bowel disease, fibrostenosis, need for surgery, and pouchitis. CBir1 flagellin (anti-CBir 1) is associated with penetrating disease, fibrostenosis, and pouchitis. Multiple positive serologic markers may predict a poor prognosis, prompting the consideration of early aggressive therapeutic interventions.[13,14]

Step Four: Obtain the Patient's Vaccination History, and Administer Appropriate Vaccinations

Treatment of IBD currently involves mesalamine; antibiotics; steroids; immunosuppressive agents, such as 6-mercaptopurine (6-MP), azathioprine (AZA), and methotrexate; and biologic agents, such as infliximab (Remicade,

Table 7. Recommended Adult Immunization Schedule

Vaccine	Dosing schedule
Td/Tdap	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years. For patients >65 years of age, administer Td booster every 10 years.
HPV	3 doses in females 12–26 years of age
Varicella	2 doses
Herpes zoster	1 dose in patients >60 years of age
MMR	1 or 2 doses in patients 19–49 years of age. 1 dose after 50 years of age if a risk factor (medical, occupational, or lifestyle) is present.
Influenza	1 dose annually
Pneumococcal (polysaccharide)	1 or 2 doses in patients 19–49 years of age if a risk factor (medical, occupational, or lifestyle) is present. 1 dose in all patients >65 years of age.
Hepatitis A virus	2 doses (6 months apart) in patients with a risk factor (medical, occupational, or lifestyle)
Hepatitis B virus	3 doses (at 0, 1, and 6 months) in patients with a risk factor (medical, occupational, or lifestyle)
Meningococcal	1 or more doses in patients with a risk factor (medical, occupational, or lifestyle)

HPV=human papillomavirus; MMR=measles, mumps, rubella; Td/Tdap=tetanus, diphtheria, pertussis.

Modified from Advisory Committee on Immunization Practices.[17]

Centocor), adalimumab (Humira, Abbott), certolizumab pegol (Cimzia, UCB), and natalizumab (Tysabri, Biogen Idec/Elan). Corticosteroids, immunosuppressive agents, and biologic agents increase the risk of infections, several of which may be preventable with vaccination.[15] For example, fulminant hepatitis and fatal varicella infection have been reported in IBD patients. Surveys have shown that few IBD patients receive recommended vaccinations, putting them at risk for avoidable infections.[16] There is no convincing evidence that vaccination of IBD patients is associated with a flare in disease activity.

Table 7 lists the recommended Advisory Committee on Immunization Practices (ACIP) Adult Immunization Schedule.[17] A vaccination history should be obtained during the first visit of a patient with Crohn's disease, and, when appropriate, vaccine titers should be checked for mumps, measles, and rubella (MMR); varicella (if the patient has no history of chicken pox); hepatitis A virus; and hepatitis B virus. Based on ACIP recommendations, prior documentable vaccination exposure, and titers, IBD patients should receive vaccination for tetanus, diphtheria, and pertussis; HPV (in women 12–26 years); influenza; pneumococcus (in select patients); meningococcus (in select patients, such as college students); hepatitis A virus; and hepatitis B virus. Hepatitis B virus testing and vaccination are necessary before initiating biologic therapy. If there are no plans to administer immunosuppressive therapy within 4–12 weeks, then live vaccines—MMR, varicella, and herpes zoster—can be administered in at-risk patients. Table 8 lists recommended inactive vaccines. Live vaccines should be avoided with medications or medical conditions that create an immunosuppressive state, as defined in Table 9.[18]

Infants receive several vaccines. The only live virus vaccination given within the first 6 months of life is rotavirus. Because serum infliximab levels may persist for 6 months in neonates born to IBD mothers who took infliximab during pregnancy, rotavirus vaccination should be avoided in these infants. Until more data are available, it appears prudent to also avoid this vaccination in infants whose mothers took anti–tumor necrosis factor agents during the third trimester of pregnancy.

Step Five: Prepare for Therapy

The mainstay of IBD therapy is anti-inflammatory and immunosuppressive treatment directed at the immune response that causes tissue damage.[19] AZA and 6-MP are widely used in IBD patients, as are biologic agents. For AZA and 6-MP therapy, pretreatment measurement of thiopurine methyltransferase (TPMT) enzyme activity or genetic testing is advised. Full doses are recommended (AZA 2.0–2.5 mg/kg or 6-MP 1–1.5 mg/kg) in patients with normal enzyme activity. Measurement of TPMT levels does not eliminate the need for routine monitoring of complete blood cell counts and liver function tests.

There are several issues in the management of immunomodulator and immunosuppressive treatment. Biologic agents should not be given when an abscess or serious infection is present. Multiple sclerosis and optic neuritis are also contraindications to treatment with biologic medications. In patients with moderate-to-severe heart failure (New York Heart Association Classes 3 and 4 congestive heart failure), infliximab is contraindicated in doses over 5 mg/kg. The annual incidence of tuberculosis in the United States is approximately 5 per 100,000 patients per year. With anti–tumor necrosis factor agents, there is a 4–90-fold increased risk of tuberculosis reactivation, usually occurring shortly after initiation of therapy.[15] Infections are often atypical, and anergy influences the sensitivity of testing. Baseline chest radiographs and tuberculin skin testing can reduce tuberculosis rates by

Table 8. Inactivated Vaccine Recommendations

Vaccine	Check titer before vaccination?	Action
Td/Tdap	No	Administer the vaccine if it has not been given over the past 10 years, or give Tdap if Td was administered ≥2 years ago.
HPV	No	3 doses at 0, 2, and 6 months in females 12–26 years of age
Influenza	No	Administer annually. Use trivalent inactivated influenza vaccine. Avoid live attenuated influenza vaccine.
Pneumococcal	No	Vaccinate if no vaccine had been given previously. 1-time revaccination after 5 years if the patient is immunosuppressed.
Hepatitis A virus	Yes	2 doses at 0 and 6–12 months or 0 and 6–18 months. Booster given >10 years.
Hepatitis B virus	Yes	3 doses at 1, 1–2, and 4–6 months. Check postvaccination titers 1 month after finishing last dose. If there is no response, revaccinate with a double dose.
Combination hepatitis A/B virus	Yes	May be given instead of individual hepatitis A virus vaccine and hepatitis B virus vaccine, particularly in individuals who do not respond to hepatitis B virus vaccination.
Meningococcal	No	Vaccinate at-risk patients if no vaccine had been given previously.

HPV=human papillomavirus; Td/Tdap=tetanus, diphtheria, pertussis.

Modified from Wasan SK, et al.[15]

up to 90%.[20] In patients with known prior exposure to tuberculosis or the bacille Calmette-Guerin vaccine, the use of quantiFERON gold assay (Cellestis Limited) has been suggested.

A standard series of blood tests should be obtained at the first visit of patients with Crohn's disease, and these tests should be repeated periodically thereafter. These tests should include measurements of iron, vitamin B12, and vitamin D levels. Patients with previous steroid exposure or extensive disease should also undergo a bone density study.

Other recommendations include screening for skin cancer and human papillomavirus–associated cervical dysplasia, as well as annual skin and gynecologic examinations.

Optional Patient Resources

A number of online resources are available if patients request additional information to better understand their disease. The Crohn's and Colitis Foundation of America's website (www.ccfa.org) contains easy-to-read information on diagnosis and disease management. Other useful resources include websites from the National Institutes of Health (http://www.nlm.nih.gov/medlineplus/crohnsdisease.html), The Foundation for Clinical Research in Inflammatory Bowel Disease (http://www.myibd.org/PatientEducation/DiseaseBasics/index.html), and various universities and medical centers (eg, http://www.mayoclinic.com/health/crohns-disease/DS00104).

Summary

The first visit of a patient with Crohn's disease is an opportunity for both the patient and gastroenterologist to prepare for various therapeutic options that may be needed.

Table 9. Expert Consensus Definition of Immunosuppression

- Treatment with glucocorticoids (> prednisone 20 mg/day equivalent or 2 mg/kg/day if <10 kg, for ≥2 weeks and within 3 months of stopping)
- Ongoing treatment with effective doses of 6-MP/AZA or discontinuation within the previous 3 months
- Treatment with methotrexate or discontinuation within the previous 3 months
- Treatment with tumor necrosis factor inhibitors or discontinuation within the previous 3 months
- Significant protein-calorie malnutrition

6-MP=6-mercaptopurine; AZA=azathioprine.

Modified from Sands BE, et al.[18]

A checklist, such as the one provided in Table 1, can help remind gastroenterologists to consider factors that enable efficient assessment of patients with Crohn's disease and facilitate initiation of appropriate therapy. The use of immunosuppressive and biologic agents requires certain assessments and testing for safe and effective treatment.

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