Accordant
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Clinical Practice Guidelines

Crohn's Disease

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Approved by:
Andrew Krueger, MD
Richard B. Colletti, MD
David T. Rubin, MD

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INTRODUCTION

The AccordantCare™ program works with health plans to assess, monitor, and support those with certain complex, chronic conditions. The focus of the program is to improve health outcomes and prevent or limit disease-related complications. AccordantCare offers unique services at no additional charge to patients, putting them in a strong position to adhere to their treatment plan.

There are several ways AccordantCare augments physicians' efforts. Through regular telephone contact, AccordantCare nurses:

- Keep patients informed about the disease process
- Coach patients in self-motivation and self-care skills
- Encourage patients to alert their physician when new symptoms arise
- Direct patients to resources that help pay for medication, transportation, home modifications, etc.
- Ensure preventive and screening measures are accomplished
- Provide emotional support to patients and caregivers
- Screen for depression
- Find local support groups

We invite physicians to make use of the services offered by AccordantCare and to suggest ways we can further patients' treatment goals. To offer feedback, get more information, ask questions or voice concerns; call toll-free 1-800-948-2497 to speak with a program representative from 8 a.m. to 9 p.m., Monday through Thursday, and from 8 a.m. to 5 p.m. on Friday, Eastern Time. Messages left after hours will be returned the next business day.

Intent of Guidelines

The purpose of this Clinical Practice Guideline is to describe current patterns of practice where there is no fully established national guideline for diagnosis and management. It is not meant to dictate care of patients. Decisions about care are made by the physician and the patient based on the individual needs of that patient.

A patient's health plan may or may not pay for the all medicines, tests, equipment, or services mentioned in this document. Benefits should be checked with the individual's health plan to assure payment.

DISEASE OVERVIEW

Costs of Crohn's Disease

It has been projected that the annual treatment costs of Crohn's disease in the United States are $3.6 billion. Mean annual costs for a Crohn's patient is $8,265, and costs for children are considerably higher than for adults.[1] Thirty-one percent of costs are

attributable to hospitalizations. Therefore, better outpatient treatment and achievement of remission offer the opportunity to reduce utilization and costs.

Definition of Crohn's Disease

Inflammatory bowel disease (IBD) is a disorder in which sustained immune activity leads to inflammation of the gastrointestinal tract. Together, Crohn's disease (CD) and ulcerative colitis (UC) comprise the two major forms of IBD.

Crohn's disease is a chronic, relapsing condition that can involve any portion of the gastrointestinal tract; however, it most often affects the distal small bowel and proximal large bowel. Inflammation affects all gut layers, from mucosa to serosa, but it is often discontinuous along the length of the GI tract. Complications include stricture, fistula and abscess. The exact etiology of CD is unknown.[2]

Prevalence of Crohn's Disease

Incidence of Crohn's disease is estimated at 30,000 cases per year in the US.[3] There are approximately 450,000 people currently living with Crohn's in this country. Despite a relatively stable incidence rate, prevalence continues to rise, which may be attributable to longer life expectancies and possible in-migration of patients.[4]

Crohn's can begin at any age, but adolescents and young adults are most susceptible.[5] There is a slight female preponderance for Crohn's disease, with a 1.2:1 female to male ratio.[2] Prevalence of Crohn's disease is greatest among Caucasians, followed by African Americans (roughly 2/3 the prevalence of whites[4]), Hispanics and Asians.[6] American Jews of European descent are 4 to 5 times more likely to develop IBD than the general population.[7]

Classification of Crohn's Disease

Several systems are used to classify CD. The Montreal classification system of Crohn's is based on the patient's age and the location and behavior of the disease.[8]

Age
A1—less than 16 years old at diagnosis
A2—17 to 40 years old at diagnosis
A3—more than 40 years old at diagnosis

Location
L1—terminal ileum
L2—colon
L3—ileocolon
L4—upper GI tract
L4+—lower GI tract and distal disease

Behavior
B1—without stricture formation, nonpenetrating
B2—with stricture formation
B3—internally penetrating
B3p—perianally penetrating

The Crohn's and Colitis Foundation of America classifies Crohn's disease according to disease location:

Ileocolitis: The most common form of Crohn's, affecting the terminal ileum and colon.[5] Symptoms include diarrhea and cramping or pain in the right lower part or middle of the abdomen, often accompanied by significant weight loss. Commonly complicated by intestinal obstruction, inflammatory mass, or abscess.[5] Crohn's limited to the colon often presents with rectal bleeding, perianal complications, and extraintestinal complications involving the skin or joints.[5]

Ileitis: Affects the ileum. Symptoms are the same as ileocolitis. Complications may include fistulas or inflammatory abscess in right lower quadrant of abdomen.

Gastroduodenal Crohn's disease: Affects the stomach and duodenum (the first part of the small intestine). Symptoms include loss of appetite, epigastric pain, weight loss, and nausea. Vomiting may indicate that narrowed segments of the bowel are obstructed.

Jejunoileitis: Produces patchy areas of inflammation in the jejunum (upper half of the small intestine. Symptoms include abdominal pain (ranging from mild to intense) and cramps following meals, as well as diarrhea. Fistulas may form. Often complicated by multiple stenoses (narrowings), bacterial overgrowth, and protein loss.[5]

Crohn's colitis: Affects the colon only. Symptoms include diarrhea, rectal bleeding, and disease around the anus (abscess, fistulas, ulcers). Skin lesions and joint pains are more common in this form of Crohn's than in others.

DIAGNOSIS OF DISEASE

The diagnosis of Crohn's disease is based on presenting symptoms, physical findings, and basic laboratory abnormalities.[9] Endoscopic, radiographic, and pathological findings can document focal, asymmetric, transmural, or granulomatous features.

Clinical History

A patient's history with Crohn's disease is usually characterized by symptomatic periods (called flares) interspersed with asymptomatic periods of varying lengths. Over time, symptomatic periods become more frequent, more severe, and last longer.

Signs and Symptoms

Characteristic symptoms reflect the underlying inflammatory process[5]:

- Chronic or nocturnal diarrhea
- Abdominal pain
  - Intermittent and colicky, most commonly in the lower abdomen
  - May be more severe and localized
  - May mimic signs and symptoms of acute appendicitis
- Weight loss
- Fever
- Rectal bleeding
- Other clinical signs[5]:
  - Pallor
  - Cachexia
  - Abdominal mass or tenderness
  - Perianal fissures, fistulae, or abscess

Extraintestinal Manifestations

Extraintestinal manifestations of Crohn's disease may be present in 30% of patients[10] including:

- Musculoskeletal problems
- Pyoderma gangrenosum and other mucocutaneous problems
- Severe ocular disease (iritis, scleritis, uveitis, conjunctivitis, episcleritis)
- Hepatobiliary problems
- Renal and genitourinary problems
- Coagulation and vascular issues
- Other complications including pancreatitis, cardiomyopathy, and amyloidosis

Lab Tests for Crohn's Disease

CBC
Liver Function Tests
Electrolytes
Erythrocyte Sedimentation Rate (ESR)[5] and/or C-reactive protein (CRP)[5]
B_{12} level

Stool Examination[5]

- Bacteria
- Ova
- Parasites
- *C. difficile*
- Lactoferrin, calprotectin
- Leukocytes

Serologic tests
Anti-Saccharomyces cerevisiae antibodies(ASCA), cBIR, and Omp-C
Anti-JCV antibody status prior to treatment with Tysabri® or during treatment with Tysabri if antibody status is unknown (using an analytically and clinically validated immunoassay).[11]

Imaging Studies
Plain abdominal film
Air contrast barium enema
Small bowel follow-through
Enteroclysis
Abdominal CT scan
Computed Tomographic (CT) Enterography
Abdominal MRI scan
Magnetic Resonance (MR) Enterography
Abdominal ultrasound

Nuclear Studies:
- Leukocyte scintigraphy
- (Radiolabeled leukocyte scan; 99mTc-WBC scintigraphy)
- Schillings test for B_{12} deficiency

Endoscopy:
- Esophagogastro-duodenoscopy (EGD)
- Colonoscopy with ileoscopy
- Sigmoidoscopy
- Endoscopic retrograde cholangiopancreatography (ERCP)
- Video capsule endoscopy (VCE), with FDA-updated indications for the PillCam® SB video capsule to include use in monitoring lesions that may indicate Crohn's disease, so it can now be used to assess response to therapy.[12]

Diagnostic and/or Assessment Criteria
Crohn's Disease Activity Index (CDAI)
Harvey Bradshaw Index

APPROACH TO MANAGEMENT OF CROHN'S DISEASE

Goals of Treatment
Treatment, both medical and surgical, is palliative with the goals of[5]:
- eliminating all disease-related symptoms;
- inducing and maintaining remission;
- avoiding long-term drug toxicity and as many side effects as possible; and
- improving the patient's quality of life.

General Approach to Management

Confirm the diagnosis, especially distinguishing between ulcerative colitis and Crohn's colitis
Confirm location(s) of disease with diagnostic tools
Evaluate the severity of Crohn's disease
Evaluate the need for medications and treatments
Monitor the patient's response to medication
Monitor for side effects of medicines and continue or modify therapy as appropriate
Monitor for disease activity and complications

Recommended Drug Therapies

Several medications have been shown efficacious for inducing and maintaining remission at different disease stages[5]:

Mild to Moderate Crohn's Disease

- 5-aminosalicylates (5-ASA), sulfasalazine, and metronidazole
- Ileocolonic disease: budesonide (ileal release)
- Colonic disease: sulfasalazine/5-ASA (evidence is weak)

Moderate to Severe Crohn's Disease

- Prednisone to induce remission (or ileal treatment with budesonide)
- Azathioprine, 6MP or methotrexate to maintain remission
- Persistent Crohn's disease, or early CD that is so severe that anti-TNF therapy is appropriate: add infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cambial®), or natalizumab (Tysabri®)

Perianal disease often requires surgery in conjunction with medical therapy using antibiotics such as metronidazole or ciprofloxacin. Azathioprine or anti-TNF therapy may be used in patients with severe perianal or enterocutaneous fistulae or who are refractory to other treatment.[13]

Multiple drugs are often used to treat moderate to severe Crohn's disease. However, the value of combining anti-TNF agents with immunosuppressants such as azathioprine or methotrexate is still being evaluated.[14] Substantial numbers of hospitalizations and surgeries can occur within three months of the decision to initiate biologic therapy, which suggests the importance of maximizing the response to the first-line agent and finding strategies to maintain the patient's initial response as long as possible.[14]

In addition to efficacy and safety, route of drug administration, convenience of the therapy's dosing regimen, and the availability of reimbursement for costs can influence a patient's success with a therapy. For example, patients preferred adalimumab administered via an integrated, autoinjection pen to subcutaneous injection using a ready-to-use, prefilled syringe because it was more convenient, considered safer, and associated with less pain.[14]

A blood test known as Stratify JCV Antibody ELISA test2 or other tests can be used to determine whether a patient has antibodies to the JC virus. The use of the JCV assay can be used as a risk-stratification tool to determine the safest group of patients for using Tysabri.[15]

Severe/fulminant Crohn's Disease

- Parenteral steroids
- IV cyclophosphamide or tacrolimus in those who do not respond to high dose steroids
- Anti-TNF agents, Tysabri

Adjunctive and/or Nondrug Therapies

Many adjunctive therapies are used to control the symptoms and adverse consequences associated with Crohn's disease. These include but are not limited to:

- Antidiarrheal agents
- Anticholinergic agents
- Parenteral vitamin B_{12}
- Cholestyramine
- Iron supplements
- Analgesics
- Probiotics[16]

Nutritional Therapy

Many IBD patients receive minimal dietary instruction despite substantial clinical practice guidelines from the American Dietetic Association, the World Gastroenterology Organization, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, the American Society for Parenteral & Enteral Nutrition and other organizations.

Nutritional therapy in Crohn's disease has the primary goal of replenishing nutrients. Although self-reported food intolerances are common, there is currently no proven correlation between particular foods and Crohn's disease.[6] Likewise, there is no consistent support for the clinical efficacy of any specific whole food diet in the management of the disease. Most gastroenterologists are flexible with diets for patients with Crohn's disease except when other conditions dictate restrictions (ie, restriction of dairy products for lactose-intolerant patients).

One large study reported that many people with IBD found that their symptoms improved with foods like yogurt, rice, and bananas. Foods associated with worsening symptoms included raw or uncooked vegetables, spicy foods, fruit, nuts, fried foods, milk, red meat, carbonated soft drinks, popcorn, dairy, alcohol, high-fiber foods, corn, fatty foods, seeds, coffee, and beans.[17]

Exclusive enteral nutrition (EEN) for children is as effective as steroids for the induction of remission.[18] It helps avoid many of the negative side effects associated with steroids

while simultaneously addressing nutritional deficits. EEN demonstrates high rates of mucosal healing and improvements in nutritional status.

Total parenteral nutrition (TPN) may be considered for patients with severe malnutrition before surgery or as a primary therapy in combination with bowel rest for selected patients with severe disease. In rare cases, patients with severe short bowel syndrome may require life-long TPN. Patients or their parents should be educated about the complications associated with TPN.

Surgical Therapies
Seventy percent of CD patients need surgery after 10 years of disease duration. Seventy to eighty percent of post-surgery patients experience a recurrence of disease within one year. Without treatment, 20% to 30% of CD patients require another surgery within five years.

The American Society of Colon and Rectal Surgeons published Practice Parameters for the Surgical Management of Crohn's Disease. While recommended, these parameters are not meant to dictate a specific form of treatment.[19]

PREVENTION AND MANAGEMENT OF COMPLICATIONS

Accordant helps patients prevent and manage complications by teaching early warning signs, encouraging adherence to treatment plans, offering supportive care, and recommending physician contact when needed. The goals and cooperative interventions listed below do not represent a comprehensive list of the complications of CD, but they do reflect some of the more common clinical situations that Accordant addresses. General health topics (eg, age-appropriate cancer screening) are beyond the scope of this document.

Goal: Promote Healthy Behavior
Cooperative interventions

- Provide educational resources that promote proper nutrition, exercise and hydration to help prevent poor skin integrity, malnutrition and other co-morbid conditions.
- Encourage patients not to smoke and provide information and education on resources that help patients to stop smoking.
- Encourage patients to plan daily activities so as to avoid stress as much as possible.
- Encourage flu vaccination/pneumococcal vaccination (polyvalent Pneumovax), unless contraindicated, to high-risk patients with CD.

Goal: Promote Self-Management of Condition
Cooperative interventions:

- Inform patients that an Accordant nurse is available for incoming calls 24 hours a day.
- Provide information on national and community-based Crohn's disease foundations and resources.
- Provide an approved list of CD educational materials and Web sites during assessments and on an as-needed basis.
- Educate patients on their treatment options, benefits, risks, and side effects, to enhance adherence through informed decision making.
- Educate patients regarding the signs, symptoms and prevention of disease flares.
- Educate patients regarding the signs, symptoms, and prevention of the common extraintestinal complications of CD.
- Evaluate the adequacy of support systems and work with physicians, patient, family, and the health plan to correct deficiencies.
- Educate and support the patient's family and/or caregiver.
- Enhance the patient's access to support groups and encourage communication with physicians.
- Educate patients about the psychosocial complications of CD.
- Assist physicians in detecting mood disturbances using a telephonic depression screening tool. Obtain the patient's consent to notify and provide his/her physician with screening results. Facilitate a corrective plan as approved by patient and physician.
- Address any financial or social barriers to physician access or medication adherence.

Goal: Stabilize Disease and Prevent Exacerbations
Cooperative interventions:

- Identify any barriers to the appropriate use of medications.
- With physician's approval, teach guidelines for the safe use of local anti-inflammatory drugs, corticosteroids, antibiotics, immunosuppressive agents and the biologic response modifiers.
- Educate patients to report the side effects of their medicines to their physician as soon as possible.
- Assess patient adherence with medications and educate patients to report any of their concerns with pain or GI symptoms to their physician immediately.
- Communicate to the patient's physician a summary of reasons for non-adherence (if any) to the treatment plan.

Goal: Prevent Infections
Cooperative interventions:

- Educate about the risks, signs and symptoms of common infections to which patients with Crohn's are prone and for which they require rapid diagnosis and treatment in order to:
    - prevent a functional deterioration related to febrile illness, and
    - minimize emergency room visits and inpatient stays.
- Educate patients to understand that they may be at increased risk for *C. difficile* infection, know the signs and symptoms of *C. difficile* infection and report any they experience to their doctor.
- Educate patients to understand that they may be at increased risk for norovirus infection, know the signs and symptoms of norovirus infection, and report any symptoms they experience to their doctor.[20]
- Educate patients to take preventive steps to eliminate *C. difficile* spores by frequent hand washing.
- For patients taking immunosuppressants, work with physician to monitor for opportunistic infections.
- Ask patients to consult with their doctor before traveling, especially if taking immunomodulators and if traveling to less-developed countries where they might be exposed to widespread opportunistic infections.
- Educate patients on the signs and symptoms related to inflammation, abscess, bowel perforation, bowel obstruction, fistula, dehydration, and toxic megacolon, and on the importance of notifying their physician as soon as possible should they have any of these symptoms.
- For women, recommend routine preventive vaccination against human papilloma virus.

Goal: Promote Early Detection of Colorectal Cancer
Cooperative interventions:

- Teach the risk factors and signs/symptoms of intestinal cancer.
- Encourage patients with extensive Crohn's colitis (at least one-third the length of the colon) for at least 8 years to discuss screening colonoscopy with their MD.
- Encourage a surveillance plan utilizing colonoscopy every 2 years.
- Explain to patients with primary sclerosing cholangitis (PSC) that they should begin surveillance colonoscopy at the time of PSC diagnosis and have yearly colonoscopy thereafter.
- Provide information to facilitate the patients' decision-making about treatment.

Goal: Prevent Complications Related to Extraintestinal Manifestations
Cooperative interventions:

- Assess patients for systemic complications involving other organs. With physician's approval, educate patients to recognize and report the signs and symptoms of
    - eye infection,
    - kidney stones,
    - urinary tract infection,
    - PSC,
    - skin changes.
- Monitor CD patients for severe iron deficiency anemia, which may be indicated by various signs and symptoms including fatigue, pallor, and difficulty breathing on exertion.
- Encourage stretching exercises, a calcium-rich antioxalate diet, smoking cessation, consistent fluid intake, management of inflammation and adherence to their medication and treatment regimen.
- Educate about pain control measures.

Goal: Promote Medication Safety
Cooperative interventions:

- Educate patients about their medication, its dosing, potential side effects, interactions, etc., and the importance of reporting any issues to their physician.
- Educate patients about tests associated with medications (e.g.,TPMT enzyme levels prior to thiopurine; JCV antibody status prior to Tysabri)[11,21]
- Inform physicians of any patient medication errors or unreported side effects.
- Encourage patients to carry all prescription and over-the-counter medications to their physician visits.
- Monitor adherence to follow-up lab work as needed for specific medications.
- Educate patients on contraindicated medications and drug-to-drug interactions.
- Advise patients of the importance of talking with their physician before stopping any prescribed therapy.

PATIENT FOLLOW-UP

Please inform Accordant of any issues that require monitoring or follow-up with your patient so that we may effectively communicate and reinforce the specifics of the physician treatment plan. For example, follow-up with the patient may be helpful after home safety evaluations, physical therapy, or the acquisition of new durable medical equipment.

With the high cost of treating Crohn's disease, ongoing follow-up with patients to evaluate their changing status is essential. Accordant can work with the patient to

coordinate referrals, community resources, and government services. We also can collaborate with other healthcare professionals on behalf of the patient.

Examples of ways that physicians can facilitate Accordant follow-up include:

- Encourage patients to work with Accordant for their education, information and self-care needs.
- Inform Accordant of the patient's unique educational needs or barriers to care so that we can supplement your activities.
- Communicate to Accordant the physician-driven treatment plan or referral needs so that we can optimally support your activities.
- Apprise Accordant of any issues that require monitoring or follow-up.
- Communicate to Accordant any strategies to prevent injury or disease complications.
- Inform Accordant that a member is considering becoming pregnant or is pregnant.
- Communicate with Accordant throughout a member's pregnancy regarding the physician treatment plan, member adherence, and any needed patient education.
- Inform Accordant of medications prescribed to the patient that require monitoring so that we can maximize patient adherence with the necessary testing.
- Communicate to Accordant any other activities that we can facilitate: for example, adult daycare services, transportation needs, assistance with obtaining drugs and supplies, etc.

PATIENT EDUCATION

List of approved websites:

The American College of Gastroenterology: http://gi.org//

Crohn's and Colitis Foundation of America: http://www.ccfa.org/

National Digestive Diseases Information Clearinghouse (NDDIC):
http://digestive.niddk.nih.gov/ddiseases/pubs/crohns/index.aspx

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