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## PRACTICE GUIDELINES

# Management of Crohn's Disease in Adults

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## PREAMBLE

Guidelines for clinical practice are intended to suggest preferable approaches to particular medical problems as established by interpretation and collation of scientifically valid research, derived from extensive review of published literature. When data are not available that will withstand objective scrutiny, a recommendation may be made based on a consensus of experts. Guidelines are intended to apply to the clinical situation for all physicians without regard to specialty. Guidelines are intended to be flexible, not necessarily indicating the only acceptable approach, and should be distinguished from standards of care that are inflexible and rarely violated. Given the wide range of choices in any health care problem, the physician should select the course best suited to the individual patient and the clinical situation presented. These guidelines are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee. Expert opinion is solicited from the outset for the document. The Committee reviews guidelines in depth, with participation from experienced clinicians and others in related fields. The final recommendations are based on the data available at the time of the production of the document and may be updated with pertinent scientific developments at a later time. (Am J Gastroenterol 2001;96:635–643. © 2001 by Am. Coll. of Gastroenterology)

## INTRODUCTION

Crohn's disease encompasses a spectrum of clinical and pathological patterns manifested by focal, asymmetric, transmural, and, occasionally, granulomatous inflammation affecting the gastrointestinal (GI) tract with the potential for systemic and extraintestinal complications (1). The incidence and prevalence in the United States remain similar to other "Westernized" countries, estimated at 5/100,000 and 50/100,000, respectively (2, 3). The disease can affect any age group, but the onset (diagnosis) is most common in the second and third decade (teenagers and young adults). Crohn's disease must be differentiated from other inflammatory bowel diseases that mimic or complicate the clinical course. Crohn's disease is neither medically nor surgically "curable" requiring therapeutic approaches to maintain symptomatic control, improve quality of life, and minimize short- and long-term toxicity and complications (4). Despite the therapeutic burden, the majority of patients do maintain long-term well-being interspersed with short intervals of morbidity (5). Despite the relatively low incidence and prevalence compared to more common GI disorders, the cost of medical and surgical therapy for Crohn's disease is estimated at up to 2 billion dollars annually in the United States (6, 7) and is increasing with the advent of newer biological approaches (8). Since the previous edition of these guidelines (9), significant advances have arisen regarding therapeutic alternatives although the volume of an appropriately derived evidence base that accounts for the disease heterogeneity and potential for site-specific therapy (10) remains relatively thin. This update follows a similar organization for therapy according to disease severity, modified where applicable to disease location.

## CLINICAL FEATURES

The heterogeneity of manifestations, a potentially insidious onset, overlapping features with other inflammatory bowel diseases, and/or presentation without GI symptoms (*i.e.*, extraintestinal symptoms), can make the diagnosis of Crohn's disease difficult. Characteristic symptoms of chronic or nocturnal diarrhea and abdominal pain, weight loss, fever, and rectal bleeding reflect the underlying inflammatory process (1). Clinical signs include pallor, cachexia, an abdominal mass or tenderness, or perianal fissures, fistulae, or abscess. Associated extraintestinal features can include inflammation of the eyes, skin, or joints and, in children, the failure of growth or retarded development of secondary sex characteristics (11, 12). Although the onset is typically insidious, occasionally, Crohn's disease can present with a fulminate onset or toxic megacolon (13). Despite the potential heterogeneity, individual manifestations and complications, there are definable patterns according to disease location (14) and type (inflammatory, fibrostenotic, or fistulizing) (15), which are important in determining clinical outcomes.

The ileum and colon are the most commonly affected sites, usually complicated by intestinal obstruction, inflammatory mass, or abscess (14, 16). The acute presentation of ileitis may mimic appendicitis and, rarely, Crohn's disease

may be limited to the appendix. Perianal manifestations are common and may precede the onset of bowel symptoms (17). Patients with Crohn's disease limited to the colon commonly present with rectal bleeding, perianal complications, and extraintestinal complications involving the skin or joints (18). Crohn's disease limited to the colon can be difficult to distinguish from ulcerative colitis (19). Diffuse jejunoileitis is a less common variant often complicated by multifocal stenoses, bacterial overgrowth, and protein-losing enteropathy (20). Gastric and duodenal manifestations include epigastric pain, nausea and vomiting, or gastric outlet obstruction (21).

Extraintestinal symptoms of Crohn's disease related to intestinal inflammation include spondylarthritis (ankylosing spondylitis and sacroiliitis), peripheral arthritis, cutaneous manifestations (erythema nodosum and pyoderma gangrenosum), ocular inflammation (uveitis or sclero-conjunctivitis), primary sclerosing cholangitis, and hypercoagulability (22). In addition, Crohn's disease also may be complicated by sequelae related to malabsorption (*e.g.*, anemia, cholelithiasis, nephrolithiasis, or metabolic bone disease). Also, there has been an increased awareness that Crohn's disease of long duration can be complicated by adenocarcinomas of the GI tract and, rarely, lymphoma (23).

## DIAGNOSIS

*The diagnosis of Crohn's disease is based upon a composite of endoscopic, radiographic, and pathological findings documenting focal, asymmetric, transmural, or granulomatous features. The sequence of diagnostic maneuvers is based upon presenting symptoms, physical findings, and basic laboratory abnormalities.*

### *General*

Crohn's disease should be considered for patients presenting with chronic or nocturnal diarrhea, abdominal pain, bowel obstruction, weight loss, fever, night sweats, or symptoms reflecting underlying intestinal inflammation, fibrosis, or fistula. Alternative inflammatory bowel diseases (infectious, ischemic, radiation-induced, medication-induced, particularly nonsteroidal anti-inflammatory drugs), or idiopathic (ulcerative colitis, celiac disease, or microscopic colitis), and irritable bowel syndrome comprise the major differential diagnoses. The presence of fecal leukocytes confirms intestinal inflammation. In the presence of diarrhea at presentation or relapse, stools should be examined for enteric pathogens, ova and parasites, and *Clostridium difficile* (24, 25). Serological studies such as antibodies against *Saccharomyces cerevisiae* are evolving to support the diagnosis of Crohn's disease (26) but may not be sufficiently sensitive or specific to be practical as screening tools (27, 28).

### *Radiological Features*

Diagnosis of Crohn's disease can be accomplished by contrast radiography (air contrast barium enema, small bowel follow through, or enteroclysis) to confirm disease location and intestinal complications (29, 30). Radiolabeled leukocyte scans can discriminate between inflammatory and noninflammatory features and may be used occasionally in clinical practice when there is a discrepancy between clinical symptoms and structural or anatomic studies (31). Abdominal or endoscopic ultrasonography, computerized tomography, or magnetic resonance imaging can delineate and discriminate intra-abdominal masses/abscesses or perianal complications (32).

### *Endoscopy*

Upper or lower GI endoscopy is used to confirm the diagnosis of Crohn's disease, assess disease location, or obtain tissue for pathological evaluation (31, 33). Endoscopic appearance has not correlated with clinical disease activity after steroid therapy (34), but there is a closer correlation between therapeutic effects and mucosal healing with chimeric anti–tumor necrosis factor (anti-TNF) monoclonal antibodies (35). Upper GI endoscopic findings of focal gastritis have recently been described that are indicative of Crohn's disease and separate from the findings related to *Helicobacter pylori* (36, 37). Colonoscopic evaluation of surgical anastomoses can be used to predict the likelihood of clinical relapse and assess response to postoperative therapy (38). Endoscopic biopsy can establish the diagnosis, differentiate between ulcerative colitis and Crohn's disease, rule out acute self-limited colitis, or identify dysplasia or cancer (31, 33).

## EXACERBATING FACTORS

Factors recognized to exacerbate Crohn's disease include: intercurrent infections (both upper respiratory tract and enteric infections, including *Clostridium difficile*), cigarette smoking (39), and nonsteroidal anti-inflammatory drugs (25). The issue of *stress* initiating or exacerbating Crohn's disease remains controversial (40). Although many patients (and family members) are convinced that stress in an important factor in the onset or course of illness, it has not been possible to correlate the development of disease with any psychological predisposition or exacerbations to stressful life events.

## DETERMINING DISEASE ACTIVITY

Therapeutic options are determined by an assessment of the disease location, severity, and extraintestinal complications. In the absence of a "gold standard" measure of disease activity, *severity* is established on clinical parameters, systemic manifestations, and the global impact of the disease on the individual's quality of life (4). Additional factors that impact on therapy include the assessment of growth and nutrition, extraintestinal complications, therapy-induced complications, functional ability, social and emotional support and resources, and education about the disease (41).

Defining Crohn's disease activity is complicated by the

heterogeneous patterns of disease location and complications, and the potential for co-existent symptoms of irritable bowel syndrome (10). No single "gold standard" indicator of clinical disease has been established. Composite indices of disease activity have been used in controlled clinical trials to provide reliable and reproducible correlates to clinicians' and patients' "global assessment of well-being" (10), but these have not been commonly employed in clinical practice. Regulatory authorities have not yet established recommendations for a single measurement of disease activity (42). However, the most recent approval for Crohn's disease therapy in the United States was based upon definitions of "clinical improvement" and "clinical remission" supported by the Crohn's Disease Activity Index (4) and "fistula closure." Other investigators have used individual therapeutic goals such as "steroid withdrawal or sparing," or "avoidance of surgery," which, although in accord with clinical decision making, suffer from patient and physician subjectivity (10). Endoscopic indices have been developed to quantify ileal and colonic lesions (43) as well as the presence of recurrent disease at surgical anastomoses (38). Instruments have also been developed to assess perianal disease (44) and quality of life (45). In general, the goal of therapy for Crohn's disease is to eliminate symptoms and to maintain the general "well-being" of patients with as few side effects and long-term sequelae as possible. Cost constraints are becoming increasingly important with the development of novel biological agents (7, 8) but have not yet entered into therapeutic decision making.

### *Working Definitions*

Since the last edition of these Practice Guidelines, the working definitions of Crohn's disease activity have not changed and are described below.

MILD–MODERATE DISEASE. Mild–moderate Crohn's disease applies to ambulatory patients able to tolerate oral alimentation without manifestations of dehydration, toxicity (high fevers, rigors, prostration), abdominal tenderness, painful mass, obstruction, or >10% weight loss.

MODERATE–SEVERE DISEASE. Moderate–severe disease applies to patients who have failed to respond to treatment for mild–moderate disease or those with more prominent symptoms of fevers, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia.

SEVERE–FULMINANT DISEASE. Severe–fulminant disease refers to patients with persisting symptoms despite the introduction of steroids as outpatients, or individuals presenting with high fever, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess.

REMISSION. Remission refers to patients who are asymptomatic or without inflammatory sequelae and includes patients who have responded to acute medical intervention or have undergone surgical resection without gross evidence of residual disease. Patients requiring steroids to maintain well-being are considered to be "steroid-dependent" and are usually not considered to be "in remission."

## MANAGEMENT

### *General*

*Therapeutic recommendations depend upon the disease location, severity, and complications. Therapeutic approaches are individualized according to the symptomatic response and tolerance to medical intervention. Therapy is sequential to treat "acute disease" then to "maintain remission." Surgery is advocated for obstructing stenoses, suppurative complications, or medically intractable disease. Narcotic analgesia should be avoided except for the perioperative setting because of the potential for tolerance and abuse in the setting of chronic disease (46).*

### *Mild–Moderate Active Disease*

*Ileal, ileocolonic, or colonic disease is treated with an oral aminosalicylate (mesalamine 3.2–4 g or sulfasalazine 3–6 g daily in divided doses). Alternatively, metronidazole 10–20 mg/kg/day may be effective in a proportion of patients not responding to sulfasalazine. Ciprofloxacin 1 g daily is equally effective to mesalamine, and controlled ileal release budesonide may become an available alternative in the near future.*

Large controlled clinical trials completed in the 1970s and 80s in the United States (47) and Europe (48) demonstrated benefits of sulfasalazine over placebo in trials lasting up to 16 wk enrolling patients with active ileocolonic and colonic Crohn's disease. Although less effective than steroids, approximately one-half of patients achieved a "clinical remission." Sulfasalazine has not been consistently effective for patients with active disease limited to the small intestine (47–50). Clinical trials have not been of sufficient size to compare sulfasalazine to alternative aminosalicylates (51). Different formulations of mesalamine also have been effective for the acute treatment of mild–moderate Crohn's disease (52–54) at doses of 3.2–4 g daily although all trials with mesalamine have not been superior to placebo (51, 55). Comparisons between mesalamine formulations have not been sufficient to discriminate between agents for ileal, ileocolonic, or colonic disease. Although commonly employed in clinical practice, neither rectal mesalamine nor rectal corticosteroids have been adequately evaluated in controlled trials to determine an ultimate role as topical agents for distal colonic disease.

Metronidazole, 10 or 20 mg/kg, was compared to placebo for mild–moderate disease and was more effective for ileocolitis and colitis than for isolated ileal disease (56). Sample sizes were insufficient to determine a dose response. Metronidazole was also compared to sulfasalazine in a 16-wk, crossover, Scandinavian trial (57). The initial response was

similar although more patients who failed sulfasalazine responded to metronidazole than *vice versa*. There are no long-term data regarding metronidazole although peripheral neuropathy has been well documented necessitating monitoring for symptoms or signs of paresthesias.

Ciprofloxacin 1 g daily has been evaluated in a short, 6-wk controlled trial and compared to mesalamine 4 g daily (58). Approximately 50% of patients in each group achieved a clinical remission. In uncontrolled trials, combinations of ciprofloxacin and metronidazole have been reported to provide superior results to either agent alone (59, 60). In contrast, controlled trials using combinations of antimycobacterial agents have not demonstrated short- or long-term efficacy (61).

In some countries, controlled-release budesonide formulations (currently not FDA approved) are used to treat mild–moderate active Crohn's disease involving the distal ileum and/or right colon (62).

The evidence base for treatment of upper intestinal (esophageal, gastroduodenal, and jejunoileal) Crohn's disease is inadequate. Symptoms of upper GI Crohn's disease have been reported (uncontrolled) to respond to acid-reduction therapy with proton pump inhibitors (63–66). Jejunoileitis is often complicated by small bowel bacterial overgrowth (21, 67), which responds to rotating antibiotics.

Response to initial therapy should be evaluated within several weeks. Treatment for active disease should be continued to the point of symptomatic remission or failure to continue improvement. Patients achieving remission should be considered for maintenance therapy. Those with continued symptoms should be treated with an alternative therapy for mild–moderate disease or advanced to treatment for moderate–severe disease according to their clinical status.

### *Moderate–Severe Disease*

*Patients with moderate–severe disease are treated with prednisone 40–60 mg daily or budesonide 9 mg daily (currently not FDA approved), until resolution of symptoms and resumption of weight gain (generally 7–28 days). Infection or abscess requires appropriate antibiotic therapy or drainage (percutaneuous or surgical). Infusions of infliximab are an effective adjunct and may be an alternative to steroid therapy in selected patients in whom corticosteroids are contraindicated or ineffective.*

No appropriate dose-ranging studies have been performed to evaluate conventional steroid dosing or dose schedules for Crohn's disease (68). Comparable clinical effects have been reported from placebo-controlled and active-comparitor trials with approximately 50–70% receiving the equivalent of prednisone, 0.5–0.75 mg/kg (or 40 mg) daily, achieving a clinical remission over 8–12 wk (47, 48, 69–71). When a clinical response has been achieved, doses are tapered according to the rapidity and completeness of response. Generally, doses are tapered by 5–10 mg weekly until 20 mg, and by 2.5–5 mg weekly from 20 mg until discontinuation (4).

Enteric coated formulations of budesonide, 9 mg daily, have been evaluated for treatment of active ileal and ileocecal Crohn's disease with consistent benefits comparable to prednisone or prednisolone, 40 mg daily (69–71), and superior to placebo (72). Steroid-related side effects are encountered less often with short-term budesonide compared to prednisolone, but some degree of adrenal suppression can be anticipated.

Over 50% of patients treated acutely with corticosteroids will become "steroid dependent" or "steroid resistant" (73), particularly smokers, or those with colonic disease (74). There are no short- or long-term benefits from the addition of an aminosalicylate to corticosteroids (48, 75, 76). Azathioprine and mercaptopurine have had demonstrable adjunctive benefits to steroids in adults but may require up to 4 months to demonstrate a beneficial effect (77). Dose-response studies have not been performed with azathioprine or mercaptopurine. Genetic polymorphisms for thiopurine methyltransferase, the primary enzyme metabolizing mercaptopurine, have been identified which may afford the potential to regulate therapy according to measurement of mercaptopurine metabolites (6-thioguanine) (78). At present, the optimal dose and mode of therapeutic monitoring remain to be established although clinical trials have demonstrated efficacy for oral azathioprine at 2.5 mg/kg (77). Intravenous loading of azathioprine does not offer a therapeutic advantage over 2 mg/kg daily dosing (79). Parenteral methotrexate, 25 mg subcutaneous or intramuscular on a weekly basis, also is effective in allowing steroid tapering for steroid-dependent patients (80).

Chimeric anti-TNF monoclonal antibody therapy with infliximab is effective for treatment of Crohn's disease patients who have not responded to aminosalicylates, antibiotics, corticosteroids, or immunomodulators (81). Improvement at 4 wk was observed in over 80% of patients treated with 5 mg/kg, and over 50% achieved a clinical remission. Retreatment is likely to be necessary on an ongoing basis to prevent relapse (82). Infliximab infusions have been associated with both acute and delayed infusion reactions including delayed hypersensitivity (serum sickness-like) reactions, particularly after prolonged intervals (>12 wk) subsequent to an initial treatment. Other adverse events include the development of antichimeric (HACA) and anti-DNA antibodies (83). It remains to be determined whether concurrent immunomodulation will improve the clinical response or reduce immunogenicity to the chimeric antibodies (83).

Although elemental diets and possibly liquid polymeric diets have demonstrable clinical benefits and reduce inflammatory features of active Crohn's disease, the long-term course of disease is not altered, compliance is difficult in adults, and the cost is considerable (84). Elimination diets are not effective at preventing relapse after elemental diets.

### *Severe–Fulminant Disease*

*Patients with persisting symptoms despite introduction of oral steroids or infliximab, or those presenting with high fever, frequent vomiting, evidence of intestinal obstruction,*

*rebound tenderness, cachexia, or evidence of an abscess should be hospitalized. Surgical consultation is warranted for patients with obstruction or tender abdominal mass. An abdominal mass should be evaluated via ultrasound or computerized tomography to exclude an abscess. Abscesses require percutaneous or surgical drainage. Once an abscess has been excluded or if the patient has been receiving oral steroids, parenteral corticosteroids equivalent to 40–60 mg of prednisone are administered in divided doses or as a continuous infusion. There is no specific role for total parenteral nutrition in addition to steroids. Nutritional support via elemental feeding or parenteral hyperalimentation is indicated, after 5–7 days, for patients unable to maintain nutritional requirements.*

Supportive or resuscitative therapy with fluid and electrolytes is indicated for dehydrated patients. Transfusions are necessary in the setting of anemia and active hemorrhage. Oral feedings may be continued, as tolerated, for patients without obstructive manifestations or severe abdominal pain. More severely ill patients or those with evidence of obstruction should be treated with bowel rest and parenteral nutritional support (85). Obstruction may be secondary to inflammatory narrowing, fibrotic stricturing or an adhesive process. Differentiation is based on evaluation of the clinical course (presence or absence of inflammatory features) and prior radiographic studies. Adhesive obstructions typically respond to nasogastric suction and, in the absence of fever or rebound tenderness, do not commonly require emergent surgery. Fibrostenotic disease may respond, initially, to bowel rest and corticosteroids but obstructive symptoms often recur with steroid tapering. In the presence of an inflammatory mass, broad-spectrum antibiotics should be instituted along with parenteral corticosteroids (86).

Parenteral corticosteroids are indicated for patients with severe–fulminant Crohn's disease (87). Dose-ranging studies have not been performed to define an optimal dose or schedule of administration although most clinicians administer parenteral corticosteroids equivalent to 40–60 mg of prednisone in divided doses or as a continuous infusion. Intravenous ACTH can be used instead of intravenous corticosteroids but is potentially complicated by adrenal hemorrhage (88). Patients who do not respond to parenteral steroids may respond to intravenous cyclosporine (89) or tacrolimus (90, 91) although there are no controlled or dose-response data. There are no data on the utility of infliximab for treatment of severe Crohn's disease.

Patients who respond to parenteral corticosteroids or cyclosporine are gradually transitioned to an equivalent oral regimen and discharged (92). Failure to respond or worsening symptoms are indications for surgical intervention.

### *Perianal Disease*

*Acute suppuration is an indication for surgical drainage with or without placement of setons. Nonsuppurative, chronic fistulization, or perianal fissuring is treated medically with antibiotics, immunosuppressives, or infliximab.*

Perianal/perirectal abscesses require surgical drainage. Nonsuppurative perianal complications of Crohn's disease typically respond to metronidazole alone (93) or in combination with ciprofloxacin (94). In the absence of controlled, maintenance trials, it appears that continuous therapy is necessary to prevent recurrent drainage (95). The safety of long-term antibiotic therapy has not been established, and patients treated with metronidazole should be monitored for evidence of peripheral neuropathy. There are no controlled data regarding immunosuppressives although several series have reported benefits from short-term treatment with cyclosoporine (89, 96, 97) or tacrolimus (90, 91). Long-term data are lacking, and most patients require chronic therapy with azathioprine or mercaptopurine (96, 97). The latter have not been assessed in controlled trials for perianal complications of Crohn's disease although several reports describe long-term improvement in perianal disease (98, 99).

A placebo-controlled trial has demonstrated benefits from a series of infliximab, 5 mg/kg, infusions at 0, 2, and 6 wk in the closure of Crohn's disease fistulae that had not responded to prior therapy with antibiotics, corticosteroids, or immunomodulatory agents (100). A total of 68% and 55% of patients achieved closure of at least one, or all fistulae for at least 4 wk. Duration of closure averaged 12 wk. Long-term strategies for re-infusion or transitioning to oral, immunomodulatory agents need to be evaluated.

### *Maintenance Therapy*

*Corticosteroids should not be used as long-term agents to prevent relapse of Crohn's disease. Azathioprine/mercaptopurine have demonstrable maintenance benefits after inductive therapy with corticosteroids. Mesalamine or azathioprine/mercaptopurine should be considered after ileocolonic resections to reduce the likelihood of symptomatic recurrence.*

Evidence continues to accumulate regarding the benefits of long-term, maintenance therapy for Crohn's disease. There continues to be confusion regarding the issues of "steroid maintenance" *versus* "steroid dependence." The former applies to (clinical trial) evidence of a therapy that prevents relapse in a population of patients. The latter is a clinical observation pertaining to individual patients unable to taper steroids below a certain dose without developing symptoms (4).

Patients treated acutely with corticosteroids are unlikely to remain well over 1 yr without some maintenance therapy (47, 73). Younger patients, those with colonic disease, and cigarette smokers are more likely to become steroid dependent (74). Yet, there is a preponderance of evidence that steroids are ineffective for maintaining remissions in Crohn's disease. This applies to conventional corticosteroids (101) as well as controlled-release budesonide (102–106).

Neither early trials using sulfasalazine (47, 48) nor subsequent trials with mesalamine (107) have demonstrated significant maintenance benefits for Crohn's disease after medically induced clinical remissions. In particular, mesalamine has not been efficacious in preventing relapse after corticosteroid-induced remissions (76). In contrast, azathioprine and mercaptopurine have been effective in allowing reduction in steroid doses and maintaining remissions after steroid-inductive therapy (108). It remains to be determined how to "optimize" dose and whether induction of leukopenia or therapeutic monitoring 6-thioguanine metabolites offer improved means of assuring a long-term response (78). Azathioprine at 2.5 mg/kg and mercaptopurine at 1.5 mg/kg have been effective after 3 to 6 months, but the duration of clinical benefits beyond 4 yr has yet to be defined (109). Complete blood counts must be monitored carefully early in the course of treatment and long term, at a minimum of every 3 months because of the risk of delayed neutropenia (110, 111). Pancreatitis, typically presenting several weeks after initiating therapy (112), occurs in approximately 3–15% of patients and recurs with re-introduction of either azathioprine or mercaptopurine. An increase risk of neoplasia has not been observed with the use of purine analogues for inflammatory bowel disease (113–115). Maintenance data are not yet available for methotrexate (116) whereas cyclosporine is not indicated for maintenance therapy of Crohn's disease (117, 118).

There continues to be an expanding body of evidence in favor of postoperative therapy to delay endoscopic and clinical recurrence of Crohn's disease (119, 120). Treatment with sulfasalazine at doses $>3$ g daily (121) and mesalamine, $\geq 3$ g daily (107), reduce the risk of postoperative recurrence for up to 3 yr in subgroups of patients. Short-term administration of high-dose metronidazole, 20 mg/kg, also can reduce the likelihood of recurrence for up to 1yr, but longer duration trials at lower, more tolerable doses are necessary to evaluate antibiotic therapy (122). Cigarette smoking has a detrimental impact upon disease recurrence adding more rationale to encourage cessation (120).

## INDICATIONS FOR SURGERY

*Surgical resection, stricturoplasty, or drainage of abscesses are indicated to treat complications or medically refractory disease.*

Surgical resection, aside from total colectomy and ileostomy for Crohn's disease limited to the colon, rarely "cures" Crohn's disease (119, 123). Nevertheless, surgical intervention is required in up to two-thirds of patients to treat intractable hemorrhage, perforation, persisting or recurrent obstruction, abscess (not amenable to percutaneous drainage), or unresponsive fulminant disease. The most common indications for surgical resection are refractory disease despite medical therapy or medication side effects (steroid dependence) (124, 125). Patients who fail to improve within 7–10 days of intensive inpatient management should be considered surgical candidates.

The ability to reduce the risk of postoperative recurrence after surgical resection no longer justifies prolongation of ineffective medical management to "avoid surgery." The primary objective of therapy for Crohn's disease is to restore the patient to health and well-being. Quality of life typically can be restored after surgical resection or stricturoplasty for Crohn's disease (126–128).

Therefore, medical therapies are acceptable only if they achieve their inductive or maintenance goals safely and effectively with a satisfactory quality of life. Neither patients nor physicians should view surgery as a "failure" when it can be the swiftest, safest, and most effective route to physical and psychosocial rehabilitation (6).

## CONTROVERSIAL ISSUES

Many unresolved questions remain regarding practice guidelines for Crohn's disease because of insufficient data and experience to make recommendations.

1. Despite expanding evidence of the carcinogenic potential of long-standing Crohn's disease, surveillance guidelines have yet to be defined.
2. Evidence regarding the safety of Crohn's disease therapy during pregnancy and lactation is needed.
3. Additional data are needed regarding optimal schedules of infusions of infliximab, duration of response, safety of long-term use, and requisites for concurrent therapies with aminosalicylates, antibiotics, steroids (or steroid sparing), and immunomodulators.
4. The optimal dose and formulation of mesalamine therapy (including potential benefits of rectal mesalamine) for acute and maintenance therapy of Crohn's disease remain to be established.
5. Optimal dosing, timing in relation to corticosteroid or anti-TNF therapy, utility of therapeutic drug monitoring, and duration of azathioprine and mercaptopurine remain to be established.
6. Dose-ranging and maintenance studies of methotrexate are needed.
7. Comparative benefits of budesonide regarding long-term efficacy, safety, and cost need to be evaluated.
8. Additional studies of antibiotics as active and maintenance (including postoperative maintenance) therapies are needed.
9. Additional studies of probiotic therapies are needed.
10. Short- and long-term studies assessing efficacy and safety of cyclosporine, tacrolimus, and mycophenolate mofetil are needed as are exploratory studies of novel immunomodulators.
11. Additional clinical data are required regarding novel biological agents targeting TNF, alternative cytokines and their receptors, and NF$\kappa$ beta.
12. Combination therapies incorporating "conventional"

and evolving therapeutic approaches require controlled clinical trials.

13. Outcome studies comparing medical *versus* surgical approaches should be performed.
14. Outcome studies assessing comparative cost–benefit assessments of alternative strategies are needed.

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