

Management of Crohn's Disease in Adults

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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 that will withstand objective scrutiny are not available, 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 quality of evidence upon which a specific recommendation is based is as follows: **Grade A:** Homogeneous evidence from multiple well-designed randomized (therapeutic) or cohort (descriptive) controlled trials, each involving a number of participants to be of sufficient statistical power. **Grade B:** Evidence from at least one large well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or well-designed meta-analysis. **Grade C:** Evidence based on clinical experience, descriptive studies, or reports of expert committees. 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.

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INTRODUCTION

Crohn's disease (CD) encompasses a multisystem group of disorders with specific clinical and pathological features characterized by focal, asymmetric, transmural, and, occasionally, granulomatous inflammation primarily affecting the gastrointestinal (GI) tract. This multisystem disorder with potential for systemic and extraintestinal complications (1) can affect any age group, but the onset (diagnosis) is most common in the second and third decades (teenagers and young adults). The incidence and prevalence of CD in the United States are rising for reasons that are unclear. The incidence and prevalence of CD in the United States are similar to other "Westernized" countries, and estimated to be 5/100,000 and 50/100,000, respectively (2).

It is important to differentiate CD from other inflammatory bowel diseases that can simulate or complicate its clinical course (1). CD is a chronic inflammatory disorder that is neither medically nor surgically "curable," requiring

therapeutic approaches to induce and maintain symptomatic control, improve quality of life, and minimize short- and long-term toxicity and complications (3). Newer goals of therapy include the induction and maintenance of mucosal (and histologic) healing (4,5) that are beginning to translate into changing the "natural history" of CD (6). Despite the relatively low incidence and prevalence of CD compared with more common GI disorders, the cost of medical and surgical therapy for patients with CD is estimated to be up to US\$2 billion annually in the United States and is increasing with the advent of newer biological approaches (7,8). Estimates of hospitalization rates for CD are difficult to estimate for the US population. The most recent data are from 1998 and have been extrapolated to US dollars in 2000. The total direct and indirect costs for CD in the US were estimated at US\$826 million and based on 84,000 in-patient hospital days and 1.3 million outpatient visits (9). Once patients are started on corticosteroids, up to 38% of patients will require surgery within 1 year thereafter (10),

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and in a recent population-based cohort study from Canada, hospitalization rates for CD are estimated to be 27/100,000 population with an estimated length of stay of 9 days, with nearly half of all hospitalizations requiring surgery (11). Since the previous edition of these guidelines (12), significant advances have been made focusing on therapeutic alternatives for patient care. As a consequence of the varied presentations of patients with CD, and the heterogeneity among patients, a comprehensive evidence-based (13) approach for each clinical scenario is not plausible. Recent guidelines regarding the management of CD have also been published from the UK (14) and Europe (15) and guidelines for using corticosteroids, immunomodulators, and infliximab have also been published from the US (16,17).

CLINICAL FEATURES

The heterogeneity of manifestations, a potentially insidious onset, the presence of overlapping features with other inflammatory bowel diseases, and/or the presentation without GI symptoms (i.e., extraintestinal symptoms), can make the diagnosis of CD difficult (1). Characteristic symptoms of chronic or nocturnal diarrhea and abdominal pain, weight loss, fever, or rectal bleeding reflect the underlying inflammatory process (the absence of rectal bleeding may suggest CD over ulcerative colitis) (18,19). Clinical signs include pallor, cachexia, an abdominal mass or tenderness, or perianal fissures, fistula, or abscess. Associated extraintestinal features can include inflammation of the eyes, skin, or joints (see below) (20) and, in children anemia, fever, the failure of growth, or delayed development of secondary sex characteristics (21) can be observed. Although the onset is typically insidious, occasionally, CD can present in a fulminant manner at its onset or with the presence of toxic megacolon (22). Despite its potential heterogeneity, individual manifestations, and complications, there are definable patterns according to disease location (23) and type (inflammatory, fibrostenotic, and fistulizing) (24) that are important in determining clinical outcomes. However, even the most recent classification system that considers age at diagnosis, disease location, and disease behavior (25) is not stable throughout the disease course, particularly regarding the phenotypic disease behavior that tends to progress to fibrostenosis or fistulization (26,27).

The ileum and colon are the most frequently affected sites, commonly complicated by intestinal obstruction, inflammatory mass, or abscess (23,28). The acute presentation of ileitis may mimic appendicitis and, rarely, CD may be limited to the appendix. In contrast to ulcerative colitis, perianal manifestations are unique to CD and may precede the onset of bowel symptoms (29). Patients with CD limited to the colon typically present with rectal bleeding, perianal complications, and extraintestinal complications involving the skin or joints (30). CD limited to the colon can be difficult to distinguish from ulcerative colitis (1). Diffuse jejunoileitis is a less common variant often complicated by multiple stenoses, bacterial overgrowth, and protein-losing enteropathy (31). This variant

of CD is more common in patients with younger age. Gastric and duodenal manifestations include epigastric pain, nausea and vomiting, and/or gastric outlet obstruction (32). Gastric biopsies demonstrating focal gastritis in the absence of *Helicobacter pylori* has been helpful in the diagnosis of CD in children with indeterminate colitis (33).

Extraintestinal symptoms of CD related to intestinal inflammation include spondylarthritis (ankylosing spondylitis and sacroiliitis), peripheral arthritis, cutaneous manifestations (erythema nodosum and pyoderma gangrenosum), ocular inflammation (uveitis, episcleritis, or sclero-conjunctivitis), primary sclerosing cholangitis, and hypercoagulability (34). In addition, CD may also be complicated by sequelae related to malabsorption (e.g., anemia, cholelithiasis, nephrolithiasis, or metabolic bone disease). There has also been an increased awareness that CD of long duration can be complicated by adenocarcinoma of the GI tract (35,36).

Natural history

Luminal CD. CD typically has a chronic, relapsing course (37) with approximately half of all patients being in clinical remission at any particular time. If an individual patient is in remission for 1 year, there is an 80% chance that this individual will remain in remission over the course of the subsequent year. For a patient who has active disease in the past year, there is a 70% chance that this patient will be active in the forthcoming year; with a 50% chance of being in remission within the ensuing 3 years. Overall, 13% of patients will have a relapse-free course, 20% have relapses of disease every year, and 67% have had a combination of years in relapse and years in remission within the first 8 years after initial diagnosis. Less than 5% of patients will have a continuous course of active disease. A subsequent population-based inception cohort of patients (prior to the introduction of anti-TNF (tumor necrosis factor) therapy into routine clinical practice) was evaluated by a Markov model, which estimated that a representative patient with CD would be expected to spend 24% of the time in medical remission (on no medications), 41% of the time in post-surgical remission (on no medications), and 27% of the time in medical treatment with a 5-ASA derivative only, whereas only 7% of the time would be spent having a disease activity/severity that mandated treatment with corticosteroids or immunomodulators (38).

Fistulizing CD. The lifetime risk of fistula development in patients with CD has been reported to range from 20 to 40% (29). In a population-based series from Olmsted County, Minnesota, the cumulative risk for the development of fistula was 33% at 10 years and 50% after 20 years, and in up to 45% of patients fistula development preceded the diagnosis of CD (39). The clinical course of fistulae is variable and depends on their location and complexity. Internal fistulas, such as enterovesical (bowel to bladder), or enteroenteric (bowel to bowel), are more difficult in general to close with medical therapy. External fistulas may be enterocutaneous (bowel to skin); this subtype of fistula represents the majority of

fistulas seen in patients with CD. A perianal fistula, then, is an abnormal connection from an internal opening to the external surface of the perianal skin. Complex fistulae rarely heal spontaneously; regardless, complete fistula closure rates of 6% (for unspecified time duration) and 13% (for at least 1 month's duration) have been reported in placebo-treated patients enrolled in randomized controlled trials of 6-mercaptopurine and infliximab, respectively. The recurrence of perianal fistulae after medical or surgical therapy is common and has been reported in referral centers to be as high as 59–82%, whereas population-based cohorts have reported a lower overall recurrence rate (Olmstead county cohort reporting only 34%) (39).

DIAGNOSIS

The diagnosis of CD is based on a composite of endoscopic, radiographic, and pathological findings documenting focal, asymmetric, transmural, or granulomatous features. The sequence of diagnostic maneuvers is based on presenting symptoms, physical findings, and basic laboratory abnormalities (grade C). Currently, the measurement of genetic mutations in patients with CD remains a research tool that is not yet proven to be of clinical benefit for the general assessment of diagnosis, guidance of patient care, or prediction of response to specific medical therapies. The use of genetic testing is currently not recommended in the caring of patients with CD (level C). Additionally, serological studies evaluating antibodies against *Saccharomyces cerevisiae*, antineutrophil cytoplasmic antibodies, antibodies directed against CBir1, OmpC are evolving to provide adjunctive support for the diagnosis of CD but are not sufficiently sensitive or specific to be recommended for use as a screening tools.

General

CD should be considered in the differential diagnosis 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 related to the use of non-steroidal anti-inflammatory drugs), or idiopathic intestinal disorders (ulcerative colitis, celiac disease, or microscopic colitis), and irritable bowel syndrome comprise the major differential diagnoses (1). The presence of fecal leukocytes (or more recently abnormal fecal concentrations of calprotectin or lactoferrin) is an excellent way to confirm intestinal inflammation or inflammation in general; sometimes the presence of intestinal inflammation is also reflected in serum acute-phase reactants (e.g., elevated erythrocyte sedimentation rate, and elevated orosomucoid, and elevated C-reactive protein). In the presence of diarrhea at presentation or relapse, stools should be examined for enteric pathogens, ova, and parasites, and *Clostridium difficile* toxin (40). Serological studies evaluating antibodies

against *S. cerevisiae*, antineutrophil cytoplasmic antibodies, antibodies directed against CBir1, OmpC (41) are evolving to provide adjunctive support for the diagnosis of CD (42) but are not sufficiently sensitive or specific to be used as screening tools (43,44).

Genetic testing. Evidence, to date, suggests that CD is likely to be a complex genetic disorder with a combination of genetic predisposition and potential environmental triggers. Thus, clinical cases we currently classify as CD likely encompass a heterogeneous subset of disorders, with differing immunopathogenic mechanisms (18). Recently, the *NOD2/CARD15* gene (IBD1 locus on chromosome 16) has been described to be associated with CD with a pattern of ileal involvement, fibrostenotic disease, an earlier age of onset, and a family history of CD. Carriage of a single copy of the risk alleles increases the risk of developing CD by 2- to 4-fold. A substantially higher risk is conferred to patients who carry two copies of the risk alleles; the risk of developing CD is 20- to 40-fold in these patients. *NOD2/CARD 15* functions to a large extent in an autosomal recessive pattern, as is exemplified by the observation that compound heterozygous or homozygous risk alleles confer a greater risk than heterozygotes or single-dose carriers. Approximately 8–17% of CD patients possess two copies of the major risk alleles for *NOD2/CARD 15*. Approximately 27–32% of patients with CD carry only one major risk allele; in comparison to 20% of Caucasian controls (45–47).

In a similar manner, a non-synonymous single nucleotide polymorphism in the *SLC22A4* gene encoding the organic cation transporter *OCTN1* has been linked with CD in Caucasian populations (a 1672CT transversion, resulting in the amino-acid substitution L503F) (48). However, the functional consequences of this alteration remain to be established. Recently, single nucleotide polymorphisms in the interleukin-23 (*IL-23*) gene have been reported in patients with inflammatory bowel disease (49). Currently, the measurement of allelic mutations in patients with CD remains a research tool that is not yet proven to be of clinical benefit for the general assessment of diagnosis, guidance of patient care, or prediction of response to specific medical therapies.

Endoscopy. Upper or lower GI endoscopy is used to confirm the diagnosis of CD, assess disease location, or obtain tissue for pathological evaluation (44). Endoscopy can also serve a therapeutic role in the dilation of strictures, particularly those at a surgical anastomosis, although double-blind, sham-controlled trials are lacking (50,51). A recent systematic review suggested that those patients who benefit most from endoscopic balloon dilation have short (less than 4 cm) postsurgical anastomotic strictures (52). The use of adjunctive corticosteroid injection into strictures at the time of balloon dilation was not effective (53).

Endoscopic appearance, to date, has not correlated with clinical disease activity after steroid therapy (54), but there is a closer correlation between therapeutic effects and mucosal

healing with anti-TNF monoclonal antibodies (55). Upper GI endoscopic findings of focal gastritis have recently been described that are indicative of CD and separate from the findings related to *H. pylori* (33). Colonoscopic evaluation of surgical anastomoses can be used to predict the likelihood of clinical relapse and assess response to postoperative therapy (56). Endoscopic biopsy can establish the diagnosis, differentiate between ulcerative colitis and CD, exclude the presence of acute self-limited colitis, or identify dysplasia or cancer (57–59). Recently, the use of video capsule endoscopy (VCE) has been assessed, and in a prospective blinded evaluation, it was demonstrated to be superior in its ability to detect small bowel pathology missed on small bowel radiographic studies and computerized tomography (CT) radiographic examinations (60). However, there is a risk of capsule retention within strictures that may require surgical intervention and the role of VCE in CD remains to be defined as a validated instrument to determine whether ulceration(s) discovered at the time of VCE are specific for CD (61,62). Retention of the VCE has been reported to occur in up to 13% of patients with CD (63). It is currently recommended that radiographic studies (small bowel follow through, CT enterography, or magnetic resonance enterography) be performed prior to VCE in patients with CD to assess for the presence of unsuspected small intestinal strictures (64,65). Small bowel strictures, which occur frequently in patients with known CD, are considered to be a contraindication to VCE for fear of capsule retention. A patency capsule, which can be administered prior to the use of a VCE to assess for the presence of significant strictures, has recently become available. The “patency capsule” is a self-dissolving capsule that is of the same size as the video capsule. It contains a radiofrequency identification tag that permits it to be detected by a scanning device placed on the abdominal wall. When its passage is blocked by a stenosis, the patency capsule dissolves in 40–80 h after ingestion.

Imaging studies

Diagnosis of CD can be accomplished by contrast radiography (air contrast barium enema, small bowel follow through, or enteroclysis) to confirm disease location and intestinal complications (44). Transabdominal ultrasound or endoscopic ultrasonography, CT, or magnetic resonance imaging (MRI) can delineate and discriminate intra-abdominal masses/abscesses or perianal complications (66). Recently, CT and MRI enterography have been used and early evaluation suggests efficacy in the evaluation of small bowel pathology in patients with CD (67–70). These modalities offer the potential to differentiate inflammatory from non-inflammatory disease. Their roles are evolving and have not been conclusively established (44). For patients requiring serial imaging, MRI may be preferred over CT to minimize cumulative risks of radiation (71).

Exacerbating factors

Factors recognized to exacerbate CD include intercurrent infections (both upper respiratory tract and enteric infec-

tions, including *C. difficile*) (2,40), cigarette smoking (2,72,73), and non-steroidal anti-inflammatory drugs (74). The issue of stress initiating or exacerbating CD remains controversial (75,76). Although many patients (and family members) are convinced that stress is 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 (77).

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” for the measurement 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 (44,78,79). 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 (77).

Defining CD activity is complicated by the heterogeneous patterns of disease, location, and complications, and the potential for coexistent symptoms of irritable bowel syndrome. 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” (13,78), but these have not been commonly used in clinical practice. Regulatory authorities have not yet established recommendations for a single measurement of disease activity. However, recent approvals for CD therapy in the United States have been based on definitions of “clinical improvement” and “clinical remission” supported by the Crohn’s Disease Activity Index (CDAI) and “fistula closure.” Recent trials with immune-modifying agents (80–82) and biologic therapies (83) have evaluated “steroid withdrawal” in patients with steroid-dependent or steroid-refractory disease (44). Endoscopic indices have been developed to quantify ileal and colonic lesions as well as the presence of recurrent disease at surgical anastomoses (78) and the achievement of “mucosal healing” in CD has been correlated with pharmacoeconomic and quality-of-life outcomes. Instruments have also been developed to assess perianal disease (29,84) and quality of life (78,85). In general, the goal of therapy for CD is to eliminate all disease-related symptoms, normalize the patients’ quality of life, and maintain the general “well-being” of patients with as few side effects and long-term sequelae as possible. In the future, the ability to modify the course of CD by reducing the evolution toward penetrating or stricturing complications may be possible with combinations of biologic and immune-modifying agents, similar to the treatment advances that have occurred for patients with rheumatoid arthritis. In addition, cost constraints are becoming increasingly important with the development of novel biological agents (8).

Although the use of biologics imposes substantial “up-front” costs, they have been demonstrated to be cost-effective in the treatment of CD by virtue of reductions in hospitalization, surgeries, and other interventions (8,86–88).

Working definitions

Since the previous editions of these Practice Guidelines, the working definitions of CD activity have not changed substantially and are now presented and are consistent with the European Crohn's and Colitis Organization's (ECCO) grading of disease activity (44). Although the majority of clinical trials have utilized CDAI to assess therapeutic outcomes (78), a more “clinical,” working definition, for CD activity is valuable for the practicing physician. This enables clinicians to guide therapy in an appropriate manner. It should be stressed that there may be various end points to consider when defining remission. An individual may be in endoscopic remission, clinical remission, or surgical remission. An individual is in symptomatic remission (usually corresponding to a CDAI <150) when that patient is asymptomatic or without any symptomatic inflammatory sequelae. Individuals included in this category may have responded to medical therapy or surgical therapy (such as ileocolonic resection) and have no residual active disease. Individuals who require the use of conventional corticosteroids to achieve clinical well-being are said to be “steroid dependent” and are not considered to be in remission. This statement is based on the potential for adverse events to accrue in patients on conventional corticosteroids. Individuals with mild–moderate disease (usually corresponding to a CDAI 150–220) are ambulatory and able to tolerate oral alimentation without manifestations of dehydration, systemic toxicity (high fevers, rigors, and prostration), abdominal tenderness, painful mass, intestinal obstruction, or >10% weight loss. Individuals who are considered to have moderate–severe disease (usually corresponding to a CDAI 220–450) are considered to have failed to respond to treatment for mild–moderate disease, or those with more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia. Finally, those individuals who are considered to have severe/fulminant disease (usually corresponding to a CDAI >450) are patients with persistent symptoms despite the introduction of conventional corticosteroids or biologic agents (infliximab, adalimumab, certolizumab pegol, or natalizumab) as outpatients, or individuals presenting with high fevers, persistent vomiting, evidence of intestinal obstruction, significant peritoneal signs such as involuntary guarding or rebound tenderness, cachexia, or evidence of an abscess.

Symptom assessment

Individual patients with other conditions may have symptoms indistinguishable from those of patients with active luminal CD. A search for other etiologies should be attempted as a general rule to ascertain whether a patient has symptoms from their CD or other conditions, such as bile salt diarrhea,

intestinal infection (e.g., *Salmonella*, *Shigella*, *Campylobacter*, and *C. difficile*), bacterial overgrowth (especially if these have had an ileocolonic resection or have known intestinal strictures), bypass from a fistula (such as a gastrocolic fistula), lactose intolerance, irritable bowel syndrome, anorectal sphincter dysfunction, food intolerance, intestinal obstruction or a stricture, accentuated gastrocolic reflex, a medication-related adverse event (such as diarrhea from an aminosalicylates), or other conditions. Although also not specific for CD activity, determination of C-reactive protein has become a useful laboratory correlate with disease activity assessed by the CDAI (45). In individuals without any observable mucosal inflammation or ulceration, consideration should be given to the aforementioned potential differential diagnostic possibilities. However, it is not necessary to have the complete absence of mucosal inflammation to entertain alternative explanations for specific symptoms or signs; there may be several coexisting conditions.

MANAGEMENT

General

Therapeutic recommendations depend on the disease location, disease severity, and disease-associated complications. Therapeutic approaches are individualized according to the symptomatic response and tolerance to medical intervention. Present therapeutic approaches should be considered sequential to treat “acute disease” or “induce clinical remission,” and then to “maintain response/remission.” Surgery is advocated for neoplastic/preneoplastic lesions, 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 (89,90).

The patients' response to initial therapy should be evaluated within several weeks, whereas adverse events should be monitored closely throughout the period of therapy. Treatment for active disease should be continued to the point of symptomatic remission or failure to continue improvement. In general, clinical evidence of improvement should be evident within 2–4 weeks and the maximal improvement should occur with 12–16 weeks. Patients achieving remission should be considered for maintenance therapy. Those with continued symptoms should be treated with an alternative therapy for mild to moderate disease or advanced to treatment for moderate to severe disease according to their clinical status.

The following sections review the specific data and recommendations for the treatment of luminal inflammatory CD. The anatomic distribution and disease activity are the factors to be considered when determining appropriate medical therapy for individual patients. The anatomic distribution of disease is important only for medications with targeted delivery systems, such as sulfasalazine, mesalamine, and enteric-coated budesonide, or where the target for the mechanism of action may be localized such as greater luminal bacterial concentrations

in the colon for antibiotics. For all other agents (parenteral or oral corticosteroids, mercaptopurine, azathioprine, methotrexate, infliximab, adalimumab, certolizumab pegol, natalizumab, cyclosporine A, or tacrolimus), therapeutic activity against CD is believed to occur throughout the entire GI tract.

Mild to moderate active disease

Ileal, ileocolonic, or colonic disease has commonly been treated in clinical practice with oral mesalamine 3.2–4 g daily (grade C) or sulfasalazine for ileocolonic or colonic disease as 3–6 g daily (grade A) in divided doses. Despite the use of oral mesalamine treatment in the past, new evidence suggests that this approach is minimally effective as compared with placebo (grade A) and less effective than budesonide or conventional corticosteroids (grade A). Alternatively, metronidazole at a dose of 10–20 mg/kg/day has been used in a proportion of patients not responding to sulfasalazine (grade C). Controlled ileal release budesonide (9 mg/day) is effective when active disease is confined to the ileum and/or right colon (grade A). Anti-tuberculous therapy has not been effective for either induction of remission or maintenance of remission in patients with CD (grade A).

Large controlled clinical trials completed in the 1970s and the 1980s in the United States (the National Crohn's Cooperative Study) (91) and Europe (the European Crohn's Cooperative Study) (92), respectively, demonstrated benefits of sulfasalazine over placebo in trials lasting up to 16 weeks for patients with active ileocolonic and colonic CD. 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 (92–94). Clinical trials have not been of sufficient size to adequately compare sulfasalazine to alternative aminosalicylates (95). Although different formulations of mesalamine have been shown to benefit patients in the acute treatment of mild to moderate CD (96–98) at doses of 3.2–4.0 g daily, several of the studies are of poor methodological quality (96,97) and a meta-analysis of three large trials with mesalamine, 4 g daily, demonstrated a statistically significant ($P=0.04$), but a non-clinically relevant difference (CDAI benefit of 18 points) compared with placebo (99). Comparisons between mesalamine formulations have not been sufficient to discriminate between agents for ileal, ileocolonic, or colonic disease. Thus, although oral mesalamine is widely used in clinical practice in the treatment of CD, controlled trials have not consistently demonstrated efficacy. Rectal applications of mesalamine or corticosteroids have never been evaluated in controlled trials in patients with distal colonic CD.

The attractive but unsubstantiated hypothesis that CD may be caused or exacerbated by bacteria has led to the use of antibiotics to treat mild–moderate luminal and perianal (see below) disease. Metronidazole, 10 or 20 mg/kg, has been compared with placebo for mild to moderate disease and was not more effective than placebo for inducing remission (100). A *post hoc* subgroup analysis indicated that metronidazole might

be effective in patients with colonic involvement (ileocolitis and colitis) (100). Metronidazole was also compared with sulfasalazine in a 16-week, crossover, Scandinavian trial (101). The initial response was similar, although more patients who failed to respond to sulfasalazine responded to metronidazole than *vice versa*. The small sample size of this trial and the relatively small therapeutic effect of sulfasalazine ($\leq 15\%$) make interpretation of this trial difficult. Two small placebo-controlled trials with metronidazole 1 g daily and metronidazole 800 mg daily in combination with co-trimoxazole did not demonstrate efficacy in the treatment of active CD (102,103). There are no long-term efficacy data regarding metronidazole. The well-documented risk of peripheral neuropathy necessitates monitoring for symptoms or signs of paresthesias. Neuropathy is typically detected in patients receiving chronic therapy, although it has been documented in patients taking large doses for short periods of time for acute infections (104). Ciprofloxacin, 1 g daily has been compared with mesalamine, 4 g daily in a 6-week controlled trial (105). In the absence of a placebo control, approximately 50% of patients in each group achieved a clinical remission. The small sample size and the relative lack of efficacy of the control group (mesalamine) make interpretation of this trial difficult. One small placebo-controlled trial reported that the addition of ciprofloxacin 1 g daily to ongoing therapy demonstrated statistically significant improvement to ongoing medical therapy for active CD (106). In contrast, a controlled trial assessing the combination of ciprofloxacin (1 g daily) and metronidazole (1 g daily) in addition to budesonide (9 mg daily) failed to demonstrate an additional benefit for patients receiving concomitant antibiotics despite a "trend" in *post hoc* analysis in favor of the supplemental antibiotics for patients with colonic disease (107). An uncontrolled trial of rifaximin, 200 mg t.i.d., reported benefits over 16 weeks in patients with active disease (108), but a small, multi-center placebo-controlled trial of 12-weeks duration failed to demonstrate superiority of rifaximin 800 mg p.o. daily or b.i.d. compared with placebo (109). Thus, although antibiotics are widely used in clinical practice for the treatment of CD (see perianal disease), controlled trials have not consistently demonstrated efficacy in the setting of luminal disease. Two small placebo-controlled trials of anti-mycobacterial therapy in combination with corticosteroid taper (after a steroid-induced remission) demonstrated efficacy for the maintenance of remission in patients receiving either clofazimine monotherapy or combination therapy with clofazimine, ethambutol, rifampicin, and dapsone (110,111). In contrast, five placebo-controlled trials using combinations of anti-mycobacterial agents alone without concurrent conventional corticosteroids have not demonstrated short- or long-term efficacy using varying combinations of medications, including rifampin, ethambutol, isoniazid, sulphadoxine, pyrimethamine, and rifabutin. The results of these studies are summarized and incorporated into a recent meta-analysis (112). A recently reported, large Australian study also failed to demonstrate long-term benefits from anti-mycobacterial therapy (113). On the basis of the nearly uniform

evidence in these controlled clinical trials, anti-mycobacterial therapy has no role in the treatment of patients with CD.

Controlled-release oral budesonide formulations at a dose of 9 mg daily have been demonstrated to be more effective than placebo (114,115) or mesalamine 4 g orally daily (116), and have similar efficacy when compared with conventional oral corticosteroids (114,117) for the treatment of disease in patients with mild–moderately active CD involving the distal ileum and/or right colon. Hence, for patients with mild–moderate CD with ileal and/or right colonic disease, controlled-release budesonide has demonstrated the best combination of short-term efficacy and safety in a series of well-controlled randomized trials. Thus, budesonide is recommended for use as the preferred primary therapy for patients with mild to moderately active CD who have disease localized to the ileum and/or right colon.

Owing to the relative infrequent occurrence of CD isolated to the esophagus, stomach, duodenum, or jejunum, there is a paucity of controlled clinical trials to determine evidence-based therapeutic recommendations. Uncontrolled series have reported symptomatic improvement for upper GI CD with use of proton pump inhibitors (118) and other systemically active therapies, such as systemic corticosteroids, azathioprine, 6-mercaptopurine, methotrexate, infliximab, adalimumab and certolizumab pegol, are used in a manner similar to their use in patients with moderate to severely active ileal or colonic disease (see below). Similarly, there is no evidence base for recommendations regarding the treatment of jejunoileitis that is often complicated by multifocal stricturing with resultant small bowel bacterial overgrowth and other nutritional consequences (119,120). Rotating antibiotics can be effective in the treatment of small bowel bacterial overgrowth, and supportive nutritional therapies (see below) are frequently required.

Moderate to severe disease

Patients with moderate to severe disease are treated with prednisone 40–60 mg daily until resolution of symptoms and resumption of weight gain (generally 7–28 days) (grade A). Infection or abscess requires appropriate antibiotic therapy or drainage (percutaneous or surgical) (grade C). Elemental diets are less effective than corticosteroids (grade A), but can avoid corticosteroid-induced toxicities. Azathioprine and 6-mercaptopurine are effective for maintaining a steroid-induced remission (grade A), and parenteral methotrexate at a dose of 25 mg/week is effective for steroid-dependent and steroid-refractory CD (grade B). The anti-TNF monoclonal antibodies, infliximab, adalimumab, and certolizumab pegol, are effective in the treatment of moderate to severely active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent (grade A). Infliximab monotherapy and infliximab combined with azathioprine are more effective than azathioprine in the treatment of patients with moderate to severe CD who have failed to respond to first-line therapy with mesalamine and/or corticosteroids (grade A). Infliximab,

adalimumab, and certolizumab pegol may be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired (grade B). The anti- α 4 integrin antibody, natalizumab, is effective in the treatment of patients with moderate to severely active CD who have had an inadequate response or are unable to tolerate conventional CD therapies and anti-TNF monoclonal antibody therapy (grade A).

No appropriate dose-ranging studies have been performed to evaluate conventional steroid dosing or dose schedules for CD. Comparable clinical effects have been reported from placebo-controlled and active-comparator trials, with approximately 50–70% of patients achieving a clinical remission over 8–17 weeks receiving the equivalent of prednisone, 0.5–0.75 mg/kg (or 40 mg) daily (91,117,121). Higher doses of prednisone (1 mg/kg) or methyl prednisolone (1 mg/kg) have had somewhat higher response rates of 80–90% (ref. (54,92)). There are no standards for corticosteroid tapering (15). 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 per week until 20 mg and then by 2.5–5 mg weekly from 20 mg until discontinuation of therapy. Owing to a significantly increased risk of osteoporosis in the setting of CD when conventional glucocorticosteroid therapy is used, a baseline DEXA scan, supplementation of calcium and vitamin D, and consideration of a bisphosphonate are warranted once corticosteroid therapy is initiated (16,17,122).

More than 50% of patients treated acutely with corticosteroids will become “steroid dependent” or “steroid resistant” (10,123), particularly smokers, or those with colonic disease (124). There are no short- or long-term benefits from the addition of aminosalicylates to corticosteroids (92,125,126). Azathioprine and 6-mercaptopurine have had demonstrable adjunctive benefits to steroids in adults (number needed to treat (NNT) = 5) (127,128). Dose–response studies have not been performed with azathioprine or 6-mercaptopurine: doses evaluated in clinical trials were 2.0–3.0 mg/kg for azathioprine and 1.0–1.5 mg/kg 6-mercaptopurine daily (17). Methotrexate, 25 mg intramuscular or subcutaneously, has also been effective in the treatment of steroid-refractory or steroid-dependent patients (NNT = 5) (129).

Genetic polymorphisms for thiopurine methyltransferase (TPMT), the primary enzyme-metabolizing azathioprine/6-mercaptopurine, have been identified that afford the potential to regulate therapy according to the measurement of azathioprine/6-mercaptopurine metabolites (6-thioguanine nucleotides) (17,130). No prospective controlled trial has compared whether dose escalation or initiation of therapy at the target dose is most advantageous with either 6-mercaptopurine or azathioprine. Current recommendations from the Food and Drug Administration (FDA) include determination of TPMT (either enzyme activity or genotype) prior to initiating treatment with azathioprine or 6-mercaptopurine (17). Although there have been no controlled trials evaluating optimal dosing by weight, TPMT genotype or enzyme activity levels, therapeutic metabolites or surrogate laboratory

measurements (mean corpuscular volume or leukocyte counts), modeling studies suggest that measurement of TPMT and dosing according to the functional enzyme activity may be most cost-effective (131). Thiopurines may require greater than 4 months (once the target dose is achieved) to derive optimal efficacy (127).

There have been several retrospective analyses performed evaluating the efficacy of measurement of 6-thioguanine nucleotides and 6-methylmercaptopurine in an effort to predict the sensitivity, specificity, positive and negative predictive values (132,133). Retrospective analyses have suggested that 6-thioguanine nucleotide levels are optimal between 250 and 400 pmol/8×10⁸ red blood count. At the present time, there are inadequate data to recommend routine measurement of these metabolites, although determination of 6-thioguanine nucleotide and 6-methylmercaptopurine levels can be helpful to assess lack of response, elevations in liver enzymes (usually associated with high TPMT levels and increased metabolism to 6-methylmercaptopurine (134)), leukopenia, or to assess patient adherence (17,130). Routine monitoring of complete blood counts, initially every 1–2 weeks, then, at least every 3 months is recommended to avoid the risk of acute or delayed bone marrow suppression (15,17).

Thioguanine, as an alternative to azathioprine or 6-mercaptopurine, has been used in some series with successful management in patients with allergic reactions or intolerance to azathioprine/6-mercaptopurine (135,136). However, there is a risk of nodular regenerative hyperplasia or venoocclusive disease of the liver (137) that may be related to increased levels of thioguanine nucleotides (135). At the present time, there are insufficient data to predict the risks of hepatotoxicity in CD patients and therapy with thioguanine cannot be recommended.

Parenteral methotrexate, 25 mg subcutaneous or intramuscular on a once weekly basis, is also effective at inducing remission and in allowing steroid tapering for steroid-refractory or steroid-dependent patients with CD (81,129). Lower doses have not been effective (129). Potential adverse events generally associated with the use of methotrexate include bone marrow suppression, including leukopenia, nausea, vomiting, hepatic fibrosis, and, uncommonly, hypersensitivity pneumonitis. A baseline chest X-ray along with monitoring of complete blood counts and liver chemistries is advocated (15,17). Hepatic fibrosis is one of the most consequential sequelae of long-term treatment with methotrexate. Risk factors for methotrexate hepatotoxicity include obesity, presence of diabetes mellitus, a prior history of excessive or long-term ethanol use, elevated baseline hepatocellular laboratory chemistries, a cumulative dose of methotrexate exceeding 1.5 g total drug dose, and daily dosing of methotrexate (138). The risk of methotrexate liver toxicity in patients with CD who do not have one or more of these risk factors is low (139). Prior to initiation of therapy with methotrexate, a liver biopsy is appropriate for patients with abnormal baseline liver chemistries, patients with one or more risk factors for hepatotoxicity, and patients who are suspected of having baseline chronic liver disease. The need

to perform a repeat liver biopsy once a cumulative dose in excess of 1.5 g is reached has not been formally assessed in controlled clinical trials in patients with inflammatory bowel disease, as the risk of methotrexate-induced hepatotoxicity in patients without known risk factors is low (139). In the absence of adequate biopsy data from patients with CD, it is recommended that the American Rheumatology Association guidelines regarding surveillance for hepatic toxicity be followed (140). These guidelines recommend that a liver biopsy be performed during therapy if a majority of aspartate aminotransferase values over 1 year (performed every 4–8 weeks) are elevated or if the serum albumin value is decreased. Furthermore, reduction in methotrexate dose is recommended in response to an elevated aspartate aminotransferase level. If moderate to severe fibrosis or cirrhosis is found, treatment with methotrexate should be discontinued.

The chimeric monoclonal antibody directed against TNF- α , infliximab, is effective in the treatment of moderate to severe CD in patients who have not responded to aminosalicylates, antibiotics, corticosteroids, or immunomodulators (15,17). Although a single infusion of infliximab at a dose of 5 mg/kg is effective at reducing signs and symptoms of CD over 4 weeks (141), an induction regimen of 5 mg/kg infusions at weeks 0, 2, and 6 followed by maintenance therapy (see below) has had significant advantages over episodic treatment strategies (55). Infliximab monotherapy and infliximab combined with azathioprine are more effective than azathioprine in the treatment of patients with moderate to severe CD who have failed to respond to first-line therapy with mesalamine and/or corticosteroids and are naïve to immunosuppressive and biologic agents (142,143). Assessment of prior tuberculosis exposure, current purified protein derivative status, and a chest X-ray prior to treatment with infliximab are important as infliximab use has been associated with reactivation of latent tuberculosis (144). Infectious complications with other organisms, particularly intracellular pathogens are also increased with anti-TNF therapy (145,146). A substantial proportion of patients with CD will be anergic (147), thus a vigilant approach to symptoms of active tuberculosis or other infections should be maintained.

Treatment with infliximab is generally well tolerated; however, infliximab infusions have been associated with both acute and delayed hypersensitivity (serum sickness-like) infusion reactions. Other adverse events include the development of antibodies to infliximab (ATI; previously termed human anti-chimeric antibody) and anti-double-stranded DNA antibodies (148–150). The development of ATIs correlates with an increased risk of infusion reactions and a shorter duration of response (149). Acute infusion reactions typically occur during or 1–2 h after a patient receives infliximab and can include headaches, dizziness, nausea, erythema at the injection site, flushing, fever, chills, chest pain, cough, dyspnea, and pruritis. Acute infusion reactions can be controlled by slowing or temporarily stopping the infusion and by giving acetaminophen 1,000 mg orally and diphenhydramine 50 mg orally or intravenously. Some clinicians routinely pretreat patients

with acetaminophen, corticosteroids, and/or diphenhydramine, although these are of unproven benefit for patients who have not had a prior infusion reaction. Delayed infusion reactions characteristically occur 3–14 days after infliximab infusions presenting with symptoms similar to serum sickness (myalgias, arthralgias, fever, rash, pruritis, dysphagia, urticaria, and headaches). These symptoms generally abate spontaneously, or occasionally require a brief course of corticosteroids (151,152). The primary risk for both acute and delayed reactions to infliximab is a hiatus between infliximab treatments (152). An induction schedule of infliximab at weeks 0, 2, and 6, as well as maintenance therapy, reduces the likelihood of ATI (and infusion reactions) as does concomitant immunosuppressive therapy (153) or pretreatment with corticosteroids (152,154). A significant percentage of patients treated with anti-TNF therapy develop positive anti-nuclear antibodies and a smaller proportion develop antibodies to double-stranded DNA (148,150). The development of symptomatic disease (i.e., drug-induced lupus) is distinctly unusual and no patient has developed renal or central nervous system involvement (155).

Alternative biologic formulations targeting TNF have also been reported to induce benefits in CD. Adalimumab, a human anti-TNF monoclonal antibody administered subcutaneously, has been approved by the FDA for the treatment of moderate to severe CD and has been demonstrated to be effective both in patients who are naïve to biologic therapy and in patients who have lost response to infliximab (150,156). The most effective induction dosing of adalimumab is 160 mg followed by 80 mg after 2 weeks (157). Subsequent maintenance dosing of 40 mg every other week in patients who respond to the initial induction doses prolongs responses and remissions (158,159). Dose escalation to 40 mg weekly may be necessary to maintain responses in some patients. Certolizumab pegol, 400 mg subcutaneously, has also been effective at inducing and maintaining clinical response (160) and remissions (161). In contrast, etanercept, a fusion protein consisting of an IgG1 Fc antibody fragment and two soluble TNF p75 receptors, was not effective in the treatment of CD at doses (25 mg subcutaneously twice weekly) that have been effective for rheumatoid arthritis (162). Adalimumab and certolizumab pegol share similar risks as infliximab, in particular infectious complications. However, due to subcutaneous administration infusion reactions and delayed hypersensitivity reactions have not been reported. Injection site reactions have been described with both adalimumab and certolizumab pegol. Similarly, concomitant immunomodulator use reduces immunogenicity, but has not impacted on 6–12 month efficacy. Although the combination of an immunomodulator with anti-TNF monoclonal antibodies reduces immunogenicity (anti-drug antibody formation) and increases serum concentrations, the risk–benefit of combination therapy in lieu of the recent reports of hepatosplenic natural killer T-cell lymphomas in young males receiving combination therapy has led to a re-evaluation of recommendations for concurrent immunomodulatory therapy with anti-TNF biologics (163–166) (see maintenance section for further discussion).

The humanized monoclonal antibody to alpha-4 integrin, natalizumab, is effective in the treatment of patients with moderate to severe CD and evidence of active inflammation (e.g., elevated C-reactive protein) who have not responded to aminosalicylates, antibiotics, corticosteroids, immunomodulators, and TNF inhibitors (167). An induction regimen of 300 mg infusions at weeks 0, 4, and 8 is recommended. Natalizumab is associated with an increased risk of reactivation of a latent virus, the human JC polyoma virus, which can lead to infection of the central nervous system called progressive multifocal leukoencephalopathy (PML) (168,169). PML is typically fatal. To minimize the risk of PML, natalizumab must be administered as a monotherapy (without concomitant immunosuppressive therapy) and patients must enroll in a mandatory safety follow-up program called the TOUCH program. Infectious complications (170) with other organisms may also be increased with natalizumab therapy. Treatment with natalizumab is generally well tolerated; however, natalizumab infusions have been associated with acute hypersensitivity infusion reactions. Other adverse events include the development of anti-natalizumab antibodies and hepatotoxicity (170).

No placebo-controlled trials of nutritional therapy for active CD have been performed. A Cochrane systematic review demonstrated that corticosteroids were more effective than enteral nutrition to induce remission in patient with active CD (odds ratio 0.3, 95% confidence interval 0.17–0.52) (171). There is no difference in efficacy between elemental and polymeric diets (171). At present time, the only appropriate use of enteral diets is as an adjunctive therapy to support a patients' nutrition.

Severe/fulminant disease

As a consequence of the acuteness and diversity of presentation of patients with severe CD and the potential for development of complications, the management decisions for these patients are based more on practicality than controlled trial evidence. Patients with persistence of Crohn's related symptoms despite introduction of conventional oral steroids or an anti-TNF (infliximab or adalimumab), or those presenting with high fever, frequent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess should be hospitalized. Surgical evaluation is warranted for patients with intestinal obstruction or who have a tender abdominal mass. An abdominal mass should be evaluated through transabdominal ultrasound, MRI scan, or CT to exclude the presence of an abscess. Abscesses require percutaneous or open surgical drainage. Once the presence of an abscess has been excluded or if the patient has been receiving oral corticosteroids, parenteral corticosteroids equivalent to 40–60 mg of prednisone daily or its equivalent are administered in divided doses or as a continuous infusion (grade C). There is no specific role for total parenteral nutrition in addition to steroids. Nutritional support through elemental feeding or parenteral hyperalimentation is indicated, after 5–7 days, for patients who are unable to maintain adequate nutritional requirements (grade C).

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 intestinal obstruction should be treated with bowel rest and parenteral nutritional support. Obstruction may be secondary to inflammatory narrowing, fibrotic strictures, 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 (172).

Recent preliminary data have suggested that CT enterography and MRI enterography may help differentiate inflammatory from fibrotic strictures (173–175). In the presence of an inflammatory mass, broad-spectrum antibiotics should be instituted along with parenteral corticosteroids (176).

Parenteral corticosteroids are indicated for patients with severe/fulminant CD (177). 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. Patients who do not respond to parenteral steroids may respond to intravenous cyclosporine (178) or tacrolimus (179), although there are no controlled or dose-response data. Low-dose, oral, cyclosporine has not been efficacious (180), although there are uncontrolled reports regarding the use of oral tacrolimus for steroid-refractory disease (181,182). There are no controlled data on the utility of infliximab, adalimumab, or certolizumab pegol in the treatment of severe CD, and uncontrolled retrospective data evaluating long-term results for the treatment of stenosing CD have been unfavorable in some reports (183).

Patients who respond to parenteral corticosteroids, cyclosporine, or tacrolimus are gradually transitioned to an equivalent oral regimen and discharged. Most will require maintenance therapy with an alternative immunomodulator such as 6-mercaptopurine or azathioprine (17,132,179,181,184). Failure to respond or worsening symptoms are indications for acute surgical intervention.

Perianal and fistulizing disease

Acute suppuration is an indication for surgical drainage with or without placement of non-cutting setons (grade C). Non-suppurative, chronic fistulization, or perianal fissuring is treated medically with antibiotics (grade C), immunosuppressives (grade C), or infliximab (grade A).

Perianal/perirectal abscesses require surgical drainage (185). Non-suppurative perianal complications of CD typically respond to metronidazole alone (186–188) or in combination

with ciprofloxacin (153). In the absence of controlled maintenance trials, it appears that continuous therapy is necessary to prevent recurrent drainage (29,153). The safety of long-term antibiotic therapy has not been established, and patients treated with metronidazole should be monitored for evidence of peripheral neuropathy and ciprofloxacin therapy can be complicated by tendonitis and tendon rupture. Other antibiotics have also been used in the treatment of perineal CD, including amoxicillin/clavulanate, trimethoprim sulfamethoxazole, levofloxacin, minocycline, and tetracycline (189). There are few controlled data regarding the inductive use of immunosuppressive treatment with cyclosporine or tacrolimus in the treatment of perianal CD. Several uncontrolled series have reported benefits from short-term treatment with cyclosporine (178,190,191) or tacrolimus (179,181,182,192). One placebo-controlled trial has been conducted with tacrolimus (193). Long-term data are lacking, and most patients require subsequent chronic maintenance therapy with azathioprine or 6-mercaptopurine (178,179,190,194). The latter has not been assessed in controlled trials for perianal complications of CD, although several reports from Europe and North America describe long-term improvement in perianal disease (29,195). Similarly, methotrexate has not been prospectively evaluated in perianal fistulizing CD, but several uncontrolled studies suggest a possible benefit (196,197).

A placebo-controlled trial has demonstrated benefits from a series of infliximab, 5 mg/kg, infusions at 0, 2, and 6 weeks in the closure of CD fistulae that had not responded to prior therapy with antibiotics, corticosteroids, or immunomodulatory agents (198). A total of 68 and 55% of patients achieved closure of at least one, or all, fistulae for at least 4 weeks. Continuation of treatment with 5 mg/kg every 8 weeks maintained the response for a median duration of 40 weeks, the duration of the trial, and complete cessation of fistula drainage persisted in over one-third of patients (199).

There are no controlled trial data for internal fistula or with alternative immunomodulatory agents, although there have been several series reporting positive outcomes from methotrexate with (200) or without infliximab (196) for perianal fistula.

Maintenance therapy

Sulfasalazine and mesalamine have not had consistent maintenance benefits after medical inductive therapy (grade A). Conventional corticosteroids should not be used as long-term agents to prevent relapse of CD (grade A). Budesonide at a dose of 6 mg/day reduces the time to relapse in ileal and/or right colonic disease, but does not provide significant maintenance benefits after 6 months (grade A). Azathioprine/6-mercaptopurine (grade B) and methotrexate (grade B) have demonstrable maintenance benefits after inductive therapy with corticosteroids. Azathioprine can maintain remissions induced by infliximab in steroid-naïve patients (grade B). Maintenance therapy with infliximab, adalimumab, and certolizumab pegol is effective (grade A). Infliximab monotherapy and infliximab combined with azathioprine are more effective than azathio-

prine for maintenance of patients with moderate to severe CD who have failed to respond to first-line therapy with mesalamine and/or corticosteroids (grade B). Maintenance therapy with natalizumab is effective (grade A). Metronidazole (grade B), mesalamine (grade C), azathioprine/mercaptopurine (grade B), or infliximab (grade B) should be considered after ileocolonic resections to reduce the likelihood of symptomatic recurrence, whereas conventional corticosteroids (grade A) and budesonide at a dose of 6 mg/day (grade B) are not effective.

Evidence continues to accumulate regarding the benefits of long-term, maintenance therapy for CD. Maintenance of clinical remissions has been demonstrated to reduce hospitalizations and the need for surgery beyond 1 year and improve patients' quality of life (3,88). There continues to be confusion regarding the issues of "steroid maintenance" vs. "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 (201).

The majority of patients treated acutely with corticosteroids are unlikely to remain well over 1 year without specific effective maintenance therapy (10,123,201). Younger patients, those with colonic disease, and cigarette smokers are more likely to become steroid dependent (124). There is a preponderance of evidence that low-dose conventional steroids are ineffective for maintaining remissions in CD (202). High-dose corticosteroids have not been evaluated as maintenance therapy (16,17). Long-term prednisone therapy can reduce relapse rates if doses are adjusted to maintain clinical remission, but at the expense of decreased bone mineral density (203) and other steroid-related toxicities (204). Budesonide, 6 mg/day, can allow withdrawal of systemic steroids for steroid-dependent patients with ileal and/or right colonic disease (205) and delay clinical relapse rates for 3–6 months (206–210), but not at 1 year (211).

Neither early trials using sulfasalazine (91,92) nor subsequent trials with mesalamine (212) have demonstrated significant maintenance benefits for CD after medically induced clinical remissions. In particular, mesalamine (at a dose of 4g daily) has not been efficacious in preventing relapse after corticosteroid-induced remissions (125). Antibiotics as an agent for maintenance of medically induced remission have not been evaluated. In contrast, azathioprine and 6-mercaptopurine have been effective in allowing reduction in steroid doses and maintaining remissions after steroid-inductive therapy (128). It remains to be determined how to "optimize" dose and whether induction of leukopenia or therapeutic monitoring of 6-thioguanine metabolites offers improved means of assuring a long-term response. Nevertheless, clinical trials have demonstrated that azathioprine at doses of 2.0–2.5 mg/kg and 6-mercaptopurine at a dose of 1.5 mg/kg have been effective at maintaining remissions for, at least, 4 years (213). Complete blood counts must be monitored carefully early in the course of treatment and in the long term, at a minimum of every 3 months, because of the risk of delayed bone marrow suppression

(e.g., leukopenia and thrombocytopenia) (214,215). Pancreatitis, typically presenting several weeks after initiating therapy, occurs in approximately 3–15% of patients and recurs with re-introduction of either azathioprine or mercaptopurine (17). The risk of lymphoma related to purine analogs has been widely debated (15,17,216,217). Aside from a potential risk of lymphoma (216), neoplasia has not been observed with the use of purine analogs for inflammatory bowel disease (218,219) and it is accepted that the documented benefits are most likely to offset a small increased risk (220). Lymphomas that have occurred during thiopurine therapy have increasingly been recognized to be related to Epstein–Barr infections (216,217,221). A rare form of natural killer cell, hepatosplenic lymphoma has recently been described associated with azathioprine therapy for CD either alone (222) or in combination with infliximab (223,224). Weekly methotrexate at a dose of 15 mg, intramuscularly, has also been demonstrated to maintain methotrexate-induced remissions (225), but optimal dosing has not been established (15,17,226,227). There is insufficient evidence to support the long-term use of calcineurin inhibitors to maintain remissions in CD (15,17).

Scheduled infusions of infliximab have been effective at maintaining remissions in both luminal (83) and fistulizing (199) CD. Maintenance therapy, scheduled every 8 weeks, is more effective than episodic dosing (152) and has been associated with prolonged mucosal healing, a novel end point in CD associated with improved pharmacoeconomic and quality-of-life outcomes (55). Regularly scheduled maintenance therapy is less immunogenic than episodic therapy (153). Infliximab monotherapy and infliximab combined with azathioprine are more effective than azathioprine for maintenance in patients with moderate to severe CD who have failed to respond to first-line therapy with mesalamine and/or corticosteroids and are naïve to immunosuppressive and biologic agents (142). Long-term monitoring for infectious complications while patients are receiving anti-TNF therapy is indicated (17,146) and the benefits and risks are acceptable when indicated for patients who have failed to respond to optimal therapy with conventional agents (228).

It remains to be determined whether patients can be "bridged" from infliximab induction therapy or infliximab maintenance therapy to long-term treatment with a thiopurine (143). There is increasing evidence that "top-down" therapy beginning with infliximab and azathioprine may offer steroid-sparing benefits for steroid-naïve patients (229). It appears that the benefit achieved with "early aggressive" ("top-down therapy") is a result of early introduction of immune-modifying therapy as thiopurines in conjunction with corticosteroids (82), infliximab monotherapy, and infliximab combined with azathioprine are more effective than azathioprine monotherapy in patients naïve to immunosuppressive and biologic agents (142).

Adalimumab, when given at doses of either 40 mg subcutaneously every other week or 40 mg subcutaneously every week is effective for maintaining remission in patients who respond to induction therapy with adalimumab (158,159). Certolizumab pegol, 400 mg subcutaneously every 4 weeks, has also been effective at maintenance of response and

remission (230,231). Natalizumab at doses of 300 mg every 4 weeks is effective for maintaining remission in patients who respond to induction therapy with natalizumab (232).

It also remains to be determined whether thiopurines or methotrexate will be optimally used as concomitant therapy with infliximab or other biologics (153,163–166,233). Both retrospective (165) and prospective data (51) have suggested that using concomitant immunosuppressants with infliximab does not augment response or remission rates in patients with CD or ulcerative colitis. Additionally, recently the use of 6-mercaptopurine or azathioprine alone or in combination with infliximab has been associated with the development of non-Hodgkin's lymphoma (216). The use of azathioprine alone or the combination of azathioprine and infliximab has also been associated with a rare form of lymphoma, hepatosplenic T-cell lymphoma (234). In clinical trials of infliximab, adalimumab, and certolizumab pegol where the biologic agent was administered as a loading dose induction regimen followed by systematic maintenance dosing, the rates of immunogenicity with and without concurrent immunomodulators were similar: infliximab 5 mg/kg 4.3% and 12.5% (235); adalimumab 0% and 3.8% (159); certolizumab pegol 4% and 10% (230) 2% and 12% (231). On the basis of all of these data, it may be reasonable to administer biologic agents as monotherapy, to maximize the risk–benefit ratio of treatment.

CD predictably recurs first, endoscopically, then clinically after an intestinal resection (56). There is a great deal of heterogeneity in postoperative scenarios and risks for recurrence (77,236), with cessation of smoking being the most consistent modifiable factor (236–238). There continues to be an expanding body of evidence in favor of postoperative therapy to delay endoscopic and clinical recurrence of CD (77,238). One trial from the 1980s demonstrated benefits from sulfasalazine at doses greater than 3 g daily (239), but most recent studies have focused on attempts at postoperative prophylaxis with mesalamine. Although early trials have demonstrated benefits for mesalamine, >3 g daily, at reducing the risk of postoperative recurrence for up to 3 years in subgroups of patients (240), more recent controlled trials have been less supportive (241,242). Overall, the ECCO consensus and a North American Pediatric Workshop support a modest overall benefit of approximately 1 in 10 patients (NNT=10) for mesalamine at delaying/preventing postoperative recurrence (77,238). Short-term administration of high-dose metronidazole, 20 mg/kg, and a 1-year course of ornidazole, 1 g/day, also reduce the likelihood of recurrence for up to 1 year (243,244). However, both agents have been poorly tolerated due to an increased risk of peripheral neuropathy such that additional studies of alternative antibiotics or additional dosing studies are required to identify a safe and effective regimen. Prednisone and prednisolone at low doses are not effective for reducing endoscopic and clinical recurrences (245,246). Budesonide at a dose of 6 mg daily was not effective at reducing endoscopic recurrences after 1 year (247). Recently, several trials have evaluated 6-mercaptopurine (50 mg/day) or azathioprine (2 mg/kg/day), which demonstrated modest benefits of the immune suppressants compared with

placebo and non-significant differences compared with mesalamine 3 g daily (241,248). A recent trial has demonstrated improved benefit with a combination of metronidazole for 3 months with 1 year of azathioprine (249). Additional dosing studies for azathioprine and/or 6-mercaptopurine are necessary to evaluate the risks and benefits, and patient stratification to assess their value at preventing postoperative recurrence (250). A recent trial has demonstrated efficacy for infliximab in the prevention of postoperative clinical and endoscopic recurrence after ileocecal resection (251). Similarly, trials of combination agents and other biologic strategies are warranted.

INDICATIONS FOR SURGERY

Surgical resection, stricturoplasty, or drainage of abscesses is indicated to treat complications or medically refractory disease (grade C). Surgical resection, aside from total colectomy and ileostomy for CD limited to the colon, rarely “cures” CD. 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), dysplasia or cancer, or unresponsive fulminant disease. The most common indications for surgical resection are refractory disease despite medical therapy or side effects of medication (steroid dependence) (15,252,253). Recently, laparoscopic techniques in selected patients have been advantageous in terms of more rapid resolution of postoperative ileus and shortened hospital stay, without increased complications compared with open surgery (252,254,255). Patients who have active luminal CD and fail to improve within 7–10 days of intensive in-patient medical management should be considered to be potential surgical candidates.

The ability to reduce the risk of postoperative recurrence after surgical resection (although less than ideal) coupled with the potential substantial benefits of appropriate surgical therapy, no longer justifies the prolongation of ineffective medical management to “avoid surgery.” The primary objective of therapy for CD is to restore the patient to health and well-being. Quality of life typically can be restored after surgical resection or stricturoplasty for CD (254,256). 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 (38,254,256).

CD of the colon treated with limited surgical resection is associated with a higher rate of recurrence than when treated with a total proctocolectomy (257–261). In practice, most physicians and patients appear to prefer avoidance of a permanent stoma by performing a limited surgical resection, despite the increased risk of recurrence, over total proctocolectomy. Formal studies of patient preferences on this question are lacking.

It is important to perform appropriate diagnostic tests, which may include colonoscopy, upper endoscopy, small bowel radiography, transabdominal imaging (such as CT, MRI), and VCE,

to confirm the diagnosis, to confirm the presence or absence of active disease, to exclude dysplasia or cancer, and to identify the presence, extent, and severity of complications, such as strictures, fistulas, and abscesses. The perioperative use of azathioprine or 6-mercaptopurine, and/or infliximab has not been demonstrated to be a risk factor for postoperative infectious complications, in contrast to corticosteroids that do increase the risk of postoperative infectious complications (262,263).

At present, there is no surgical technique that reduces the risk of postoperative recurrence of CD. Histologic disease at the surgical resection margins does not predict a greater risk of recurrence (264).

Strictureplasty has been advocated as an important alternative to resection in the treatment of selected fibrotic strictures of the small bowel and should be attempted when possible to help avoid impaired nutrient absorption, bile salt diarrhea, steatorrhea, bacterial overgrowth, and short bowel syndrome. The rationale for the use of this technique is that it corrects obstructive strictures while preserving functional intestinal length. Where there are multiple strictures in a short segment and where bowel length is sufficient to avoid short bowel syndrome, resection may be preferable. The use of conventional stricturoplasties (Heineke-Mikulicz stricturoplasty form) is considered appropriate when small bowel stricture lengths are <10 cm in length. This is the most widely accepted form of stricturoplasty. Longer strictures, up to 25 cm, may be treated by side-to-side stricturoplasty. The bowel is arranged in a U-shape and the mesenteric edges of the bowel are approximated. This has been termed the Finney stricturoplasty. In general, stricturoplasty for colonic disease is not recommended.

Patients with CD may develop abdominal abscesses. The presence of active luminal CD with a concomitant abdominal abscess should preferably be managed with antibiotics, percutaneous or surgical drainage followed by delayed intestinal resection if necessary. There are no controlled data to indicate whether percutaneous or surgical drainage should always be followed by a delayed resection; however, most series favor a delayed resection (265–267).

There is growing use of laparoscopically assisted surgery in patients with CD with the goals of potentially decreasing adhesion formation, postoperative pain, and hospital stay, and improving the cosmetic outcome. Whether laparoscopic resection gives benefits in addition to a shorter scar remains to be established. Experience from other laparoscopic operations (cholecystectomy and fundoplication) illustrates that once studies are performed such that they are patient and observer blinded, differences in length of stay and postoperative pain diminish. Nevertheless, patients generally prefer the minimally invasive surgical approaches.

CONTROVERSIAL ISSUES

Many unresolved questions remain regarding practice guidelines for CD because of insufficient data and inadequate experience to make formal recommendations.

- (i) Novel end points for successful medical therapy, including the potential to modify long-term disease behavior and long-term disease outcome, and prognostic factors to predict evolution of the natural history of disease are needed.
- (ii) Additional trials to compare “top-down” vs. “step-up” therapy with appropriate patient selection are needed.
- (iii) The optimal dose and formulation of mesalamine therapy (including potential benefits of rectal mesalamine) for acute and maintenance therapy of CD remain to be established.
- (iv) Additional studies of antibiotics as active and maintenance (including postoperative maintenance) therapies are needed.
- (v) Long-term studies to evaluate the safety and efficacy of budesonide at maintaining remissions at doses above 6 mg are needed.
- (vi) Studies to optimize thiopurine antimetabolite dosing are needed.
- (vii) Dose-ranging and maintenance studies of methotrexate are needed.
- (viii) Studies to define optimal approaches to minimize immunogenicity to evolving biologic therapies are needed.
- (ix) Natalizumab has been efficacious in clinical trials, but safety concerns need to be clarified (163,167,232,268–270).
- (x) Despite expanding evidence of the carcinogenic potential of long-standing CD, surveillance guidelines have yet to be defined.
- (xi) Additional studies of probiotic therapies and alternative therapies are needed (77).
- (xii) Additional clinical data are required regarding novel biological agents targeting alternative cytokines and their receptors.
- (xiii) Outcome studies comparing medical vs. surgical approaches should be performed.
- (xiv) Outcome studies assessing comparative cost-benefit assessments of alternative strategies are needed.

CONFLICT OF INTEREST

Stephen B. Hanauer has declared he has served as: consultant for Abbott Labs, Alevan, Amgen, Asahi, Astra Zeneca, Bristol Myers Squibb, Centocor, Chemocentryx, Elan, Ferring, Genentech, Glaxo Smith Kline, McNeil PPC, Millenium Pharmaceuticals, Novartis, Proctor & Gamble, Prometheus, Salix, Shire, Therakos, and UCB Pharma; clinical researcher for Abbott Labs, Asahi, Bristol Myers Squibb, Centocor, Chemocentryx, Elan, Ferring, Genentech, Novartis, Proctor & Gamble, Prometheus, Salix, Shire, and Therakos; and speaker for Centocor, Ferring, Proctor & Gamble, Prometheus, and Salix. Gary R. Lichtenstein has declared he has served as a consultant for Abbott Corporation Bristol-Myers Squibb, Astra-Zeneca, Centocor, Elan, Proctor & Gamble, Prometheus Laboratories, Salix Pharmaceuticals, Schering-Plough Corporation, Shire Pharmaceuticals, and UCB Corporation;

conducted research for Abbott Corporation Bristol-Myers Squibb, Centocor, Procter & Gamble, Prometheus Laboratories, Salix Pharmaceuticals, Shire Pharmaceuticals, and UCB Corporation; and received honoraria for lecturing from Abbott, Centocor, Elan, Procter & Gamble, Prometheus Laboratories, Salix Pharmaceuticals, Schering-Plough Corporation, Shire Pharmaceuticals, UCB Corporation. William Sandborn has served as a consultant for Abbott Laboratories, Astra Zeneca, LP, Centocor, Elan Pharmaceuticals, Inc., Ferring Pharmaceuticals A/S, Procter & Gamble, Prometheus Laboratories, Salix Pharmaceuticals, Inc., Schering Plough Corporation, Shire Pharmaceuticals, Tillotts Pharma AG, and UCB Pharma; and received research honoraria from Abbott Laboratories, Astra Zeneca, LP, Centocor, Elan Pharmaceuticals, Procter & Gamble, Salix Pharmaceuticals, Schering Plough Corporation, Shire Pharmaceuticals, Tillotts Pharma AG, and UCB Pharma.

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