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CROHN'S DISEASE: AN UPDATE

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INTRODUCTION

Crohn's disease (CD) is a chronic relapsinginflammatory bowel disease (IBD). It is characterizedby a transmural granulomatous inflammationwhich can affect any part of the gastrointestinaltract, most commonly the ileum, colon or both [1]Crohn's disease is characterizedby relapsing and remitting chronic intestinal inflammationin a genetically susceptible host. It is closely related to ulcerativecolitis, but is distinguished by key features including anatomicdisease location and clinical expression. There is significant heterogeneityin the clinical manifestations of Crohn's disease,which may involve any part of the digestive tract, may includenoncontiguous segments of inflammation (i.e., "skip lesions")with intervening normal segments of bowel, and can lead tofibrostenosing and perforating complications from transmuralinflammation. [2,3] The diversity of the clinical manifestations of Crohn's diseaselikely has its underpinnings in the disease's heterogeneous genetic profile . To date, over 150 susceptibilityor protective genes have been associated with Crohn's disease. Several of these genes encode distinct proteins critical toepithelial barrier function, immunological pathways involved incell-surface microbial recognition and antigen processing,intracellular signaling pathways implicated in immune activation,T-cell signaling, autophagy, and several other mechanismsof immune regulation [4].Despite biological treatment beingassociated with an improved health-related qualityof life, patients stillreport significant impediment on lifestyle anddaily activities during both flares and remissions. The mortality amongst patients with CD has been persistently higherthan the general population with a meta-analysis showing a pooled estimate for the standardizedmortality ratio of 1.52 [5,6,7].

EPIDEMIOLOGY

Despite many methodologic limitations, distinct andreproducible geographic and temporal trends in incidencehave been observed. A north-south gradient has reported inFranceand the United States.This observation has beenlinked to variations in exposure to sunlight,with increasinglevels of sunlight and vitamin D exposure inversely associatedwith epidemiologic and individual risk of Crohn'sdisease.Incidence rates as high as 20.2 and 12.7 per 100,000 person-years have been reported in North America andEurope, respectively,whereas in Asia, the incidence rate hasremained low, with a mean estimated incidence of 0.54 per100,000 person-years.Incidence

rates in Australia and NewZealand are comparable to those found in other parts of thedeveloped world, at 29.3 and 16.5 per 100,000 person-years.In all regions of the world where incidence has been recordedover time, the annual occurrence of new cases of Crohn's disease is rising,including the United States.[8,9,10,11,12,13,14,15]

A PubMed search reveals that the number of publications dealing with CD increased from 2 in the 1970s to more than 40 in the years from 2010 to 2014. This corroborates the opinion of all gastroenterologists on the panel that CD is increasingly being diagnosed in India. Although it is often stated that the incidence of CD is increasing in India, there is no community-based incidence or prevalence data on CD in India, and it is not possible to say whether the apparent rise in frequency of diagnosis is due to an increasing incidence of the disease in India, or due to increasing recognition of the disease by physicians.[16]Studies throughout the world have shown a small excessrisk of Crohn's disease among women. Most reports show a female-to-male ratio in adult patients between unity and1.3 : 1.In the pediatric population this is reversed, withmore boys having Crohn's disease than girls.Crohn's disease is diagnosed most often among persons 15to 30 years of age, although the age at diagnosis can rangefrom early childhood throughout one's lifespan. Populationbasedstudies have shown the median age of diagnosis to be approximately 30 years.[9,17,18,19]

ETIOPATHOGENESIS

Many infectious agents have been proposedas the cause of Crohn's disease, including chlamydia, Listeria monocytogenes, cell-wall–deficient Pseudomonas species, reovirus, and many others. Increasingly, evidence suggests that anintestinal dysbiosis exists in Crohn's disease, and which mayprecede the onset of disease. Primarily, there is a decrease indiversity of the microbial flora, with a notable reduction in Firmicutes. In particular, Faecalibacteriumprausnitzii has beenshown to be depleted in in the ileocolonic mucosa of patients with Crohn's disease. [20]

Among the most enduring hypotheses is that Mycobacterium paratuberculosis is the causative agent of Crohn's disease.[21]

The argument for a genetic predisposition to IBD begins withthe observation that family members of affected persons areat greatly increased risk for developing IBD. The relative riskamong first-degree relatives is 8 to 10 times higher than thatof the general population.[22]Ethnicity also plays a role. Eastern European (Ashkenazi)Jews are at a 2- to 4-fold higher risk of developing IBD thannon-Jews of the same geographic location. Only very rare forms of IBD are transmitted throughMendelian inheritance.

A landmark study provided deep insight into the geneticarchitecture and causation of IBD by combining data frommore than 75,000 cases of Crohn's disease and UC, controls, and results from 15 GWA studies.[23]Among 163 IBD loci identified,110 were associated with both diseases, 30 were classifiedas Crohn's disease–specific, and 23 as UC-specific.[23]However, biological differences are also suggestedby the observation that 2 risk loci, NOD2 and PTPN22,are protective for UC. Additionally, 113 of the 163 risk loci arecommon to other complex immune-mediated diseases, such astype 1 diabetes, ankylosing spondylitis, and psoriasis.[23]The discovery of the association of NOD2/CARD15with Crohn's disease has opened a remarkable window intothe pathogenesis of Crohn's disease.It hasbeen estimated that as many as 20% to 30% of patients withCrohn's disease bear abnormal NOD2/CARD15.

Beyond NOD2, multiple genetic defects in the autophagypathway, which is implicated in the pathogenesis of Crohn'sdisease, also provide a link to defective host-microbe interactions. [24,25]First, the autophagy-related 16-like 1 (ATG16L1) gene and the second autophagy gene associatedwith Crohn's disease is the IRGM (immunity-related GTPase [guanosine triphosphatase] family member M) geneon chromosome 5q33.1.[26]Thisminor allele is protective against Crohn's disease.

Even with notable progress in GWA studies, identified geneticrisk factors account at best for only 25% of disease variance.[27]rising incidence of Crohn's disease over many decades, andin developing countries, highly suggests an environmentalcontribution to the expression of disease. Epidemiologicstudies have examined numerous risk factors for Crohn'sdisease. Most studies have found breast-feeding to be protectivefor IBD. Occupations associatedwith outdoor physical labor is relatively underrepresentedamong patients with Crohn's disease.

Crohn'sdisease has been associated with higher socioeconomic status,presumably because of relative underexposure to diverseenvironmental antigens in the course of childhood—thehygiene hypothesis as it relates to intestinal mucosal immunity in IBD.

There is an increased risk of Crohn's disease among women who use oral contraceptives. [11] NSAIDs have been implicated not only inexacerbations of IBD but also as a potential precipitant ofnew cases.

Smoking is one of the more notable environmental factorsfor IBD. UC is largely a disease of ex-smokers and nonsmokers, whereas Crohn's disease is more prevalent amongsmokers.[28]

The interaction between effector T cells and APCs is critical tothe pathogenesis of Crohn's disease. Inflammation normally is kept in check through an activeprocess termed immune tolerance. The nature of theco-stimulatory signal, the type of APC, and the cytokinemilieu influence the differentiation of T cells into populationsof effector T cells, which are involved in harmful immuneresponses, and regulatory T cells, which ameliorate theimmune response.[29]

PATHOLOGY

Focal intestinal inflammation is the hallmark pathologicfinding in Crohn's disease. This tendency for inflammation tobe focal is evident in focal crypt inflammation, focal areas ofmarked chronic inflammation, the presence of aphthae and ulcers on a background of little or no chronic inflammation, and the interspersing of segments of involved bowel withsegments of uninvolved bowel. Even within a single biopsyspecimen, one can see a pronounced variability in the degreeof inflammation. The presence of focally enhanced gastritis, characterized by a focal perifoveolar or periglandularlymphomonocyticinfiltrate, is a common finding in patients withCrohn's disease. This finding underscores the focal nature of the inflammation; despite the strong potential for inflammationto occur anywhere along the entire longitudinal axis of the GI tract. To a certain extent, the nature of the findings andthe depth of inflammatory changes depends on the chronicityof the inflammation. The earliest characteristic lesion of Crohn's disease is the aphthousulcer. In the small intestine, aphthous ulcersarise most often over lymphoid aggregates, with destructionof the overlying M cells. In the colon, aphthae can occurwithout an endoscopically visible central erosion and may be associated with lymphoepithelial complexes.[30]The presence of granulomas, while highly characteristicof Crohn's disease, is neither unique to Crohn's disease

nor universally found.[31]Non-caseating granulomas, like aphthouslesions, are believed to be an early finding.

Large ulcers, sinus tracts, and strictures are late features ofCrohn's disease. Sinuses and fistulas represent extensions offissures; sinus tracts end blindly, and fistulas enter epitheliallinedorgans, such as bowel, skin, bladder, or vagina.58 Fibrosis is another transmural aspect of the disease. Fibrosismay be evident grossly as irregular thickening of the bowelwall and, along with hypertrophy of the muscularis mucosa, can contribute to the development of strictures.[32]

CLINICAL FEATURES

CD is a clinical diagnosis formed by correlationof clinical signs and symptoms, objective datafrom imaging including endoscopic with histologicinformation as well as laboratory studies[33]. Chronic diarrhoea,defined as a decrease in faecal consistencyfor more than 4 weeks [34],is the most common presenting symptom. Abdominal pain (70%), weight loss (60%)and blood, mucus or both in stools (40–50%) arealso common findings in CD [35]. Extraintestinal manifestationsaffect approximately a third of patients withIBD [36]. The most commonly observedextraintestinal manifestation is primary peripheralarthritis (33%); aphthous stomatitis, uveitis,erythema nodosum and ankylosing spondylitiscan be seen whilst pyoderma gangrenosum, psoriasisand primary sclerosing cholangitis are relativelyuncommon [37]. Fistulae, a complication of CD,occurs in up to 35% of patients with CD, with perianal fistula occurring in 20% [38]. These clinical features associated with diseaseactivity were found to contribute to 37% ofhealth-related quality-of-life (HRQOL) in a systematicreview analysing determinants of HRQOLin CD [39]. According to apatient-reported qualitative analysis [6], there is impact on lifestyle in regards totaking regular medication, restricting diet andavoiding certain trigger foods, as well as impacton daily activities where patients report absencefrom employment or school during acute flares due to pain and fatigue.

COMPLICATIONS

Intestinal complications

• Proximal gastrointestinal involvement is a complication, or a different disease presentation which may occur more often in children and in some adult ethnic groups (African-Americans, Ethiopians), and more commonly in children [40].
• Hemorrhage
• Bowel perforation
• Intra-abdominal abscesses
• Strictures and obstruction
• Fistulas and perianal disease
— These are a hallmark of CD
• Toxic megacolon
— This is a relatively rare, life-threatening complication of colitis (characterized by dilation of the colon diagnosed on plain abdominal radiography) that requires aggressive medical therapy and urgent surgical intervention if there is no response within 24 h (more common in UC than CD).
• Malignancy
— There is a significantly increased risk of colon cancer in UC later than 8 years after the diagnosis and with uncontrolled disease activity. The overall rates of colorectal cancer in UC have been decreasing in recent reports [41], perhaps due to better use of drugs that reduce inflammation over time (chemoprevention) and also because of optimized surveillance [42,43].

— Primary sclerosing cholangitis (PSC) is also increased in CD, although it is more common in UC.
— There is an increased risk of small-bowel adenocarcinoma in small-bowel CD, but it is rare.

Extraintestinal complications
• Extraintestinal complications should be differentiated from extraintestinal manifestations, and they may be related to disease or to drugs used for IBD — e.g., drug-induced arthropathies (corticosteroids, biologicals); ocular complications (corticosteroid-induced glaucoma or cataracts); hepatobiliary complications (gallstones, fatty liver); renal complications (drug-induced tubulointerstitial nephritis); anemia (iron or vitamin B12 deficiency, or thiopurine-induced cytopenia); bone complications (osteoporosis and fractures); venous thromboembolic disease; and mood and anxiety disorders.
• They affect up to 25% of those with IBD, although 15–20% have arthralgias, while the remainder have frank inflammatory disease in other organ systems. Some complications may antedate the diagnosis of IBD, and some may run an independent course from the IBD (even colectomy in UC does not affect the course of ankylosing spondylitis or primary sclerosing cholangitis — although for many, arthralgia activity parallels the activity of the bowel disease). [44]

DIAGNOSIS
The diagnosis of CD is based on a composite of endoscopic, radiographic, and pathological findings documenting focal, asymmetric, transmural, or granulomatous features. The use of genetic testing is currently not recommended in the caring of patients with CD. 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
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 [45]. Serological studies evaluating antibodies against *S. cerevisiae*, antineutrophil cytoplasmic antibodies, antibodies directed against CBir1, OmpC [46] are evolving to provide adjunctive support for the diagnosis of CD [47] but are not sufficiently sensitive or specific to be used as screening tools [48,49].

Genetic testing
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. 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 [50,51,52].

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. Currently, the measurement of allelic mutations in patients with CD remains a research tool that is not proven yet.

Endoscopy

Upper or lower GI endoscopy is used to confirm the diagnosis of CD, assess disease location, or obtain tissue for pathological evaluation [50]. 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 [53,54]. A recent systematic review suggested that those patients who benefit most from endoscopic balloon dilation have short (less than 4 cm) postsurgical anastomotic strictures [55]. The use of adjunctive corticosteroid injection into strictures at the time of balloon dilation was not effective [56].

Endoscopic appearance, to date, has not correlated with clinical disease activity after steroid therapy [57], but there is a closer correlation between therapeutic effects and mucosal healing with anti-TNF monoclonal antibodies [58]. 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* [59]. Colonoscopic evaluation of surgical anastomoses can be used to predict the likelihood of clinical relapse and assess response to postoperative therapy [60]. 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 [61,62,63]. 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 [64].
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 [65]. 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 [65]. For patients requiring serial imaging, MRI may be preferred over CT to minimize cumulative risks of radiation [71].

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. Surgery is advocated for neoplastic/preneoplastic lesions, obstructing stenoses, suppurative complications, or medically intractable disease. [72,73]

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.

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.

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).Although different formulations of mesalamine have been shown to benefit patients in the acute treatment of mild to moderate CD [74,75] at doses of 3.2–4.0 g daily, several of the studies are of poor methodological quality [75,76].

Ciprofloxacin, 1 g daily has been compared with mesalamine, 4 g daily in a 6-week controlled trial [77]. In the absence of a placebo control, approximately 50% of patients in each group achieved a clinical remission.

An uncontrolled trial of rifaximin, 200 mg t.i.d., reported benefits over 16 weeks in patients with active disease [78], 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 [79].
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 [80,81]. But 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 [82,83] or mesalamine 4 g orally daily [84]. 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.

Uncontrolled series have reported symptomatic improvement for upper GI CD with use of proton pump inhibitors [85] and other systemically active therapies, such as systemic corticosteroids, azathioprine, 6-mercaptopurine, methotrexate, infliximab, adalimumab and certolizumabpegol, are used in a manner similar to their use in patients with moderate to severely active ileal or colonic disease. Rotating antibiotics can be effective in the treatment of small bowel bacterial overgrowth, and supportive nutritional therapies 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). Infection or abscess requires appropriate antibiotic therapy or drainage (percutaneous or surgical). 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).

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).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 [86]. Infectious complications with other organisms, particularly intracellular pathogens are also increased with anti-TNF therapy [87,88].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) [89,90].

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 [91,92].

Certolizumabpegol, 400 mg subcutaneously, has also been effective at inducing and maintaining clinical response [93] and remissions [94]. 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 [95].

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 who have not responded to aminosalicylates, antibiotics, corticosteroids, immunomodulators, and TNF inhibitors [96]. An induction regimen of 300 mg infusions at weeks 0, 4, and 8 is recommended.

Severe/fulminant Disease

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. Abscesses require percutaneous or open surgical drainage. 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. Obstruction may be secondary to inflammatory narrowing, fibrotic strictures, or an adhesive process. Fibrostenotic disease may respond, initially, to bowel rest and corticosteroids but obstructive symptoms often recur with steroid tapering [97].In the presence of an inflammatory mass, broad-spectrum antibiotics should be instituted along with parenteral corticosteroids [98].

Parenteral corticosteroids are indicated for patients with severe/fulminant CD [99]. Patients who do not respond to parenteral steroids may respond to intravenous cyclosporine [100] or tacrolimus [101], although there are no controlled or dose–response data. There are no controlled data on the utility of infliximab, adalimumab, or certolizumabpegol in the treatment of severe CD. [102].

Patients who respond to parenteral corticosteroids, cyclosporine, or tacrolimus will require maintenance therapy with an alternative immunomodulator such as 6-mercaptopurine or azathioprine [103,104,105]. 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 [106]. Non-suppurative perianal complications of CD typically respond to metronidazole alone or in combination with ciprofloxacin [107]. Other antibiotics have also been used in the treatment of perineal CD, including amoxicillin/clavulanate, trimethoprim sulfamethoxazole, levofloxacin, minocycline, and tetracycline [108]. There are few controlled data regarding the inductive use of immunosuppressive treatment with cyclosporine or tacrolimus in the treatment of perianal CD.

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. Maintenance therapy with infliximab, adalimumab, and certolizumabpegol is effective (grade A). Infliximab monotherapy and infliximab combined with azathioprine are more effective than azathioprine 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.

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)

[109,110]. 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 [111,112]. 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.

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