Management of Extraintestinal Manifestations and Other Complications of Inflammatory Bowel Disease

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The past 18 months have seen many studies of the prevalence, pathogenesis, and treatment of the extraintestinal manifestations of inflammatory bowel disease (IBD). Inhibitors of tumor necrosis factor alpha have shown effectiveness in randomized trials for the treatment of spondyloarthropathies and ocular manifestations. Open-label studies suggest that these agents may be effective for pyoderma gangrenosum as well. The epidemiology of primary sclerosing cholangitis (PSC), and its relationship to IBD, is becoming clearer. Colorectal neoplasia in PSC remains an important clinical problem. Osteoporosis occurs more commonly in IBD, but the relative importance of corticosteroid use versus underlying chronic bowel inflammation as risk factors remains controversial. Chromoendoscopy may be an important means to improve detection of colorectal neoplasia in IBD. Observational studies suggest that prolonged use of aminosalicylates is associated with decreased risk of neoplasia, but data are conflicting. A randomized trial of ursodeoxycholic acid in PSC showed decreased risk of colorectal neoplasia in patients receiving the drug relative to those on placebo.

Introduction

The "extraintestinal manifestations" (EIMs) of inflammatory bowel disease (IBD) have historically referred to immune-mediated changes of the joints, spine, eye, skin, and hepatobiliary tract; however, these could be more broadly defined to include pathophysiologic sequelae of extensive bowel inflammation, such as osteoporosis and thromboembolism. Another feared complication of long-standing ulcerative colitis (UC) or Crohn's disease is the development of malignancy. This article reviews recent studies in these areas.

The mechanisms behind the observed associations between IBD and the classic EIMs remain unclear. A genetic basic for these associations remains a strong possibility. EIMs often cluster in the same individuals. In a study from Oxford, IBD patients with rheumatologic EIMs were considerably more likely than other IBD patients to have dermatologic and ocular EIMs as well, and overlap in HLA associations among the various EIMs was frequently noted [1]. One could surmise that the prevalence of EIMs would be higher in familial than in sporadic IBD. In a series of consecutive patients seen in the IBD Clinic at Mayo Clinic, Rochester, the overall prevalence of at least one classic EIM was 40%, significantly higher than the 14% prevalence seen among clinic patients without IBD who served as matched control subjects [2•]. The prevalence of classic EIMs in patients and their first-degree relatives was 23%, and this was no higher among familial IBD patients and their relatives than in sporadic IBD patients and their relatives [2•]. The prevalence of autoimmune disorders (*eg*, type 1 diabetes mellitus, autoimmune thyroid disease, and others) in the IBD patients was 10%, significantly lower than the 19% prevalence noted in the clinic controls. The prevalence of autoimmune disorders in IBD patients and their relatives was 14%, and no significant differences in prevalence were noted between the familial and sporadic groups [2•]. This study confirmed the association between IBD and classic EIMs but did not demonstrate that familial patients were more likely than sporadic patients to develop extraintestinal complications.

Just as environmental factors such as cigarette smoking and appendectomy play a role in the development and expression of IBD, these factors may also influence the development of EIMs. In a large Italian series of patients with UC, the prevalence of EIMs was significantly higher among smokers (39%) than in nonsmokers (22%), and when individual EIMs were examined, significant associations persisted for spondyloarthropathies (SpA) and dermatologic EIMs [3•]. Similarly, the prevalence of EIMs among UC patients who had undergone appendectomy was significantly higher (50%) than among those without a history (23%), again with significant associations seen for joint and skin complications but not for ocular or hepatobiliary manifestations [3•].

Musculoskeletal Extraintestinal Manifestations

The arthritic manifestations of IBD have been classified into the axial manifestations of ankylosing spondylitis (AS) and sacroiliitis, and the peripheral arthritis associated with IBD. The distinctions between these conditions are blurring. All of these entities are considered subtypes of SpA, and many patients with AS may also have peripheral arthropathy. In a study of three population-based European IBD cohorts, the prevalence of any musculoskeletal symptom was 31% in UC and 36% in Crohn's disease [4]. The prevalence of any rheumatologic manifestation in the aforementioned Mayo series was 26% [2•].

Ankylosing spondylitis and sacroiliitis

A wide variety of conditions, including AS, sacroiliitis, and inflammatory back pain, fall into the category of SpA. The prevalence of sacroiliitis and AS in IBD has varied greatly across studies due to different study populations and different definitions of these conditions. For example, in a population-based study of insurance claims data from Manitoba, Canada, the prevalence of AS ranged from 0.7% to 5.7% depending on the underlying subtype of IBD and the rigor of the algorithm to define AS [5]. In a multicenter study of three European population-based cohorts, 18% of IBD patients met criteria for SpA, but only 3% met criteria for AS [4]. A population-based study of SpA from southeastern Norway, which included a thorough rheumatologic evaluation in most patients, estimated an AS prevalence of 2.6% in UC and 6% in Crohn's disease [6]. The Mayo study found an AS prevalence of 3.7% [2•]. The prevalence of sacroiliitis in IBD tends to be lower when it is clinically defined and higher when it is radiographically defined. For example, in some of the population-based studies, the prevalence of sacroiliitis was 2% to 3%, but the diagnosis was based on plain films of the sacroiliac joints [4,6]. A recent study of consecutive IBD patients who underwent CT of the sacroiliac joints showed a much higher prevalence (23% overall and 45% among those with back pain) [7].

The relationship between SpA, intestinal inflammation, and classic IBD is complex. It has been recognized for almost 20 years that many AS patients who have no gastrointestinal symptoms have low-grade ileal inflammation [8]. In some cases, only acute inflammatory changes are encountered, but in others, the pattern of inflammation is very similar to that seen in Crohn's ileitis, and approximately 5% to 10% of idiopathic AS patients with this intestinal lesion eventually develop symptomatic Crohn's disease [9]. A recent study of first-degree relatives of Icelandic AS patients found that 41% of the relatives, and only 12% of their spouses, had subclinical intestinal inflammation (defined by elevated fecal calprotectin concentrations), suggesting genetic susceptibility to intestinal inflammation [10]. Relatives with intestinal inflammation were significantly more likely to have asymptomatic sacroiliitis on CT [10].

Mean concentrations of IgA antibodies to *Saccharomyces cerevisiae* (ASCA) in Belgian patients with AS and undifferentiated SpA were noted to be significantly higher than those seen in rheumatoid arthritis patients, perhaps pointing to the importance of subclinical ileal inflammation in these conditions [11]. However, the prevalence of positive antibody tests (>20 U/mL) was similar among the groups studied, and there were no differences in IgG ASCA levels [11]. The results of studies of NOD2/CARD 15 mutations in SpA have been conflicting. Whereas most studies have failed to detect an increase in NOD2 variants among SpA patients [12–14], preliminary studies suggest that certain subsets of patients with SpA, such as those with isolated sacroiliitis or subclinical intestinal inflammation, are significantly more likely to carry NOD2 mutations [15].

Infliximab, a monoclonal chimeric antibody to tumor necrosis factor (TNF)-α, has shown therapeutic benefit in randomized controlled trials in AS [16,17]. Etanercept, a dimeric fusion protein of the p75 TNF-α receptor and the Fc portion of IgG, has also demonstrated significant efficacy in AS in several randomized controlled trials [18–20]. A consensus conference of the Canadian Rheumatology Association reviewed, in evidence-based fashion, the use of anti–TNF-α therapies in SpA [21•]. This group concluded that infliximab and etanercept were indicated for treatment of moderately to severely active SpA patients who had not responded adequately to full doses of at least two nonsteroidal anti-inflammatory drugs, and that anti–TNF-α monotherapy was indicated for at least 1 year [21•]. Sulfasalazine and methotrexate could be considered for patients with predominantly peripheral manifestations [21•].

Peripheral arthritis

As mentioned previously, many patients with predominantly peripheral involvement also show evidence of axial involvement when they are carefully examined, and peripheral arthritis could be considered a form of SpA. The prevalence of peripheral arthritis in a population-based cohort of IBD patients from southeastern Norway was 12% by patient report, but only 3.5% by physical examination [22]. In the European multicenter study, the prevalence was 6.1% in UC and 1.7% in Crohn's disease [4]. It has become evident over the past decade that two forms of peripheral IBD-related arthritis exist. Type I is the classic asymmetric, oligoarticular arthritis with predominantly large joint involvement, and its activity tends to mirror the activity of the underlying bowel disease [23]. Type II is a symmetric polyarticular arthritis with predominantly small joint involvement, and its activity is often independent of the underlying bowel disease activity [23]. The two subtypes appear to have different HLA associations, with DRB1*0103, B*35, and B*27 seen more often in type I arthritis and B*44 seen more often in type II [24]. A peripheral arthritis similar to type I has been reported in patients with pouchitis following ileal pouch–anal anastomosis [25].

Treatment of peripheral arthritis is similar to that described for AS. In an open-label study of rofecoxib, a selective cyclooxygenase-2 inhibitor, in IBD patients with peripheral arthropathy or arthritis, only three patients (9%) withdrew because of gastrointestinal symptoms [26•], simi-

lar to what has been described retrospectively in a series from Mayo Clinic [27]. Rofecoxib was effective in controlling arthritic symptoms in 41% of the group [26•].

Dermatologic Extraintestinal Manifestations

The two major dermatologic EIMs are pyoderma gangrenosum (PG) and erythema nodosum (EN). Although the latter condition results in painful symptoms, usually in the lower extremities, during an exacerbation of IBD, its activity generally mirrors the activity of the underlying IBD, and treatment directed at bowel inflammation is often sufficient for EN. It is the former condition, PG, that is more challenging to treat, because its activity is often completely independent of the underlying bowel inflammation. PG results in ulcerating skin lesions that frequently occur on the lower extremities.

The prevalence of EN in the population-based study from Manitoba ranged from 0.6% to 11.9% depending on the case definition [5]. In a series from Oxford, the prevalence of EN was 1% in UC and 6% in Crohn's disease [1]. In the Mayo series, the self-reported prevalence of EN was 2% [2•]. EN is generally more common in women, with a female-to-male ratio as high as five to one in some studies [1].

The prevalence of PG in the Manitoba study ranged from 0.7% to 12.8%, depending on the case definition [5], whereas the prevalence in the Mayo series was 0.4% [2•]. Over a 20-year period, the frequency of PG among hospitalized IBD patients in an Israeli referral center was 0.6% [28].

The mechanism of the association between IBD and the dermatologic EIMs remains unclear. A study of NOD2/CARD15 mutations in 20 IBD patients (all but two with Crohn's) with PG revealed heterozygosity for one of the three variants in 20%, a prevalence that is no higher (and perhaps is lower) than expected [29].

Most recent studies of the dermatologic EIMs have focused on the treatment of refractory PG. First-line therapy has consisted of systemic corticosteroids, followed by tacrolimus or cyclosporine for treatment failures. Topical tacrolimus may be helpful in selected patients [30]. Several case series have described the efficacy of infliximab in adult and pediatric patients with refractory PG [31,32,33•].

Ocular Extraintestinal Manifestations

The ocular EIMs in IBD, which were recently reviewed [34], are classified by the location of ocular inflammation; they include episcleritis, scleritis, uveitis, and rare EIMs such as retinitis or optic neuritis. In the Manitoba study, the prevalence of uveitis or iritis ranged from 0.9% to 5.6% depending on the case definition [5]. In the Oxford series, the prevalence of ocular inflammation was 5% in Crohn's and 3% in UC, and the female-to-male ratio was over two to one [1]. Iritis was observed in 60%, scleritis in 30%, and uveitis in 10% of patients [1]. In the Mayo series, 4.9% of patients with IBD reported a history of ocular inflammation [2•]. Episcleritis typically results in redness and irritation, but it is not a vision-threatening complication. However, scleritis may impair vision, and to the untrained observer, it can be difficult to distinguish the two entities. Uveitis is a potentially vision-threatening complication of the iris or posterior components of the eye, and typically it is diagnosed with a slit lamp examination. Thus, it is important to refer IBD patients with ocular complaints to an ophthalmologist for diagnosis and treatment.

Several studies of therapy for ocular inflammatory conditions have been published recently. A retrospective examination of a small series of patients with acute anterior uveitis who were treated with sulfasalazine showed significant reduction in the number of flares in the year after sulfasalazine therapy, compared with the previous year (from 3.4 to 0.9 flares/year) [35]. Methotrexate was used as a steroid-sparing agent in a series of 39 patients with uveitis or scleritis [36]. Although one quarter of these patients discontinued the medication due to side effects, 79% of the remaining patients had a complete or partial response, and about one quarter of all patients had a complete response [36]. Two open-label studies of mycophenolate mofetil in the treatment of refractory ocular inflammation suggested response rates of 65% to 70% [37,38]. Two open-label studies of infliximab for refractory ocular inflammation demonstrated high response rates [39,40], although one patient developed intra-ocular and systemic tuberculosis [39]. Although etanercept was associated with good response in an open-label study [41], a recent small randomized trial of etanercept versus placebo to prevent recurrent uveitis was negative [42]. A p55 TNF receptor fusion protein appeared to be effective in an open-label study of refractory posterior uveitis [43]. The monoclonal antibody to the interleukin-2 receptor, daclizumab, has been used in two open-label studies of refractory ocular inflammation, and response rates ranged from 60% to 80% [44,45].

Hepatobiliary Manifestations

The most important hepatobiliary EIM associated with IBD is primary sclerosing cholangitis (PSC). The overall prevalence of PSC in Olmsted County, MN in the year 2000 was 21 cases/100,000 persons in men and 6 cases/100,000 in women [46•]. Approximately 75% of these patients had concomitant IBD [46•]. The prevalence of PSC in UC has ranged from 2% to 7% in most series. In the Manitoba study, the prevalence was 0.3% to 3.7% depending on the case definition [5]. The mechanism of this relationship remains unclear.

One study noted that PSC–IBD patients were more likely than UC patients without PSC to have more extensive colitis and to require less immunosuppression to control disease [47]. Furthermore, the PSC–IBD patients were more likely to have developed colorectal dysplasia or cancer [47]. This study confirms observations made previously at Mayo Clinic [48,49,50•]. The prevalence of rectal sparing and backwash ileitis appears to be higher in PSC–IBD than in typical UC

[48,49,50•]. These differences in presentation and natural history suggest that PSC–IBD may be a unique phenotype.

No major randomized controlled trials of medical therapy for PSC have been published recently. A retrospective examination of PSC patients from Norway suggests that a subgroup, perhaps 15% overall, may respond at least partially to corticosteroids [51]. Some of these patients appeared to have features of autoimmune hepatitis [51]. However, this retrospective, non-randomized experience should be interpreted cautiously. A small pilot study of etanercept showed no improvement in biochemical parameters, but 40% of those patients with pruritus noted significant improvement in this troublesome symptom [52].

No medical therapies have been proved effective in slowing the progression of PSC, and many patients ultimately require orthotopic liver transplantation (OLT). Managing IBD in the post-transplant setting can be challenging, because many PSC–IBD patients may experience flares of disease despite immunosuppression, and up to 20% of PSC patients without IBD develop the condition after transplant [53]. Colorectal cancer in IBD patients after OLT continues to be a significant issue. One recent study of 152 patients with PSC who underwent OLT noted the development of colorectal cancer in eight (5.3%), compared with seven cancers among 1184 non-PSC patients (0.6%) [54]. The cumulative risk of colorectal cancer was 14% 5 years after OLT, and 17% at 10 years if the colon was intact at the time of OLT [54].

Osteoporosis and Fracture Risk in Inflammatory Bowel Disease

Patients with IBD are at increased risk for osteopenia (bone mineral density [BMD] between 1 and 2.5 SD below mean peak bone mass) and osteoporosis (BMD less than 2.5 SD below mean peak) relative to the general population. Recently this topic was examined in detail in a technical review [55•]. Several gastroenterology societies have recently issued practice guidelines on the prevention, diagnosis, and treatment of osteoporosis in patients with IBD [56,57].

A recently published 2-year follow-up to a population-based study of BMD in Crohn's disease and UC patients from Norway illustrated that bone metabolism is a dynamic process [58]. Roughly 22% to 27% of IBD patients showed significant decreases in BMD over time, whereas 42% to 46% had significant increases in BMD. Overall mean BMD did not change [58]. A large Canadian multicenter cross-sectional study of BMD in people aged over 50 years (n=7753) examined the relationship between self-reported chronic diseases and low BMD or vertebral deformities [59]. A total of 437 patients identified themselves as having IBD; curiously, the study could not demonstrate an independent association between IBD and low BMD [59].

The causes of low BMD in IBD continue to be investigated. It is difficult in most observational studies to separate the potentially deleterious effect of corticosteroid use from that of high inflammatory activity. For example, in the population-based Norwegian study, C-reactive protein levels were significantly higher in those patients with bone loss, suggesting that disease activity may influence bone metabolism [58]. Corticosteroid use was only weakly associated with bone loss [58]. A small longitudinal study of IBD patients saw no decrease in BMD over time, and erythrocyte sedimentation rate was inversely associated with BMD [60]. Steroids were not associated with low BMD [60]. In a population-based cohort of premenopausal women from Manitoba who were diagnosed with IBD in childhood or adolescence, average BMD was normal, and the prevalence of osteoporosis was only 4% [61]. This same group of women was found to have an average intake of calcium and vitamin D that is less than recommended; however, individual differences in intake did not appear to correlate with changes in BMD [62]. Similar findings of higher than expected vitamin D deficiency and insufficiency, but a lack of correlation with BMD, were seen in a Canadian multicenter study [63].

Most [64,65] but not all [66] previous studies have suggested that IBD patients are at increased risk of bone fracture relative to the general population. A small regional cohort of UC patients from Olmsted County, MN reported a 30% increase in the risk of hip, spine, or wrist fractures, but this increase was not statistically significant [67]. However, a very large case–control study (over 231,000 pairs of fracture cases and non-fracture controls) from the General Practice Research Database (GPRD) in the UK suggested that vertebral fractures were 72% more likely to occur, and hip fractures 59% more likely in IBD patients [68•]. The risk of hip fracture was higher in Crohn's disease than in UC. Even after corticosteroid use was taken into account, IBD patients with more symptoms were significantly more likely to develop fracture, again highlighting that bowel disease activity may be an important cofactor [68•]. In a matched cohort study of over 16,000 IBD patients and over 82,000 control subjects from the GPRD, the risk of hip fracture was increased by 49% in UC and by 108% in Crohn's disease relative to controls [69•]. Furthermore, cumulative dose and current use of corticosteroids were associated with an increased risk, although in most cases this was not statistically significant [69•]. A case–control study of patients from Manitoba with IBD-associated fractures suggested a relationship between corticosteroid use and fracture risk, but this was not statistically significant [70].

Treatment of osteoporosis and osteopenia in patients with IBD mostly has been extrapolated from the postmenopausal osteoporosis literature and has focused on calcium/vitamin D supplementation and oral bisphosphonates [55•]. Recently, several small trials of medical therapy for bone disease specifically in IBD patients have been published. A randomized trial of oral calcium and vitamin D supplementation compared with intravenous pamidronate plus calcium and vitamin D was performed in 74 IBD patients with low BMD [71]. Although both groups gained BMD over the course of the 12-month study, the changes were significant only in the group that had received combi-

nation therapy, with mean increases of 2.6% at the spine and 1.6% at the hip [71]. In another randomized trial, 84 Crohn's disease patients with low BMD received oral calcium and vitamin D, sodium fluoride plus calcium/vitamin D, or intravenous ibandronate plus calcium/vitamin D [72]. Significant increases in BMD of 5.7% and 5.4% were noted in the sodium fluoride- and ibandronate-treated patients, respectively, but no significant increase was observed in the group receiving calcium and vitamin D alone [72].

Thromboembolism in Inflammatory Bowel Disease

It has been long recognized that venous thromboembolism occurs more frequently in IBD, and this topic was recently reviewed [73]. A population-based study from Manitoba estimated an annual incidence of 0.5% in IBD patients [74]. An attempt to quantify the magnitude of increased risk of thrombosis in IBD patients relative to the general population and in patients with other chronic illnesses was performed in a hospital-based study from Vienna [75•]. The risk of venous thromboembolism was assessed by questionnaire in groups of patients with IBD, rheumatoid arthritis, and celiac disease, as well as in healthy control subjects [75•]. The prevalence of a history of thromboembolism was 6.2% in patients with IBD, 2.1% in those with rheumatoid arthritis, 1.0% in those with celiac disease, and 1.6% in control subjects, yielding a greater than threefold elevation in risk relative to controls [75•]. In a case series of IBD-related thromboembolism from Mayo Clinic, colonic involvement and active IBD were common, although most patients had other risk factors for thrombophilia, including immobility, hospitalization, surgery, or malignancy [76]. In the patients who underwent comprehensive thrombophilia evaluations, fully one third had evidence of a specific thrombophilia, although none of these individually appeared to be more common than what would have been expected in the general population [76]. An evaluation of thrombopoietin levels in IBD revealed elevations in mean levels as a whole, but no differences in levels were seen between those with or without previous thromboembolic events [77].

Colorectal Neoplasia Risk in Inflammatory Bowel Disease

The risk of colorectal neoplasia (dysplasia and cancer) in IBD is well established. A meta-analysis of all available observational studies suggested that the cumulative risk of colorectal cancer is 8% after 20 years of UC and 18% after 30 years of disease [78]. A meta-analysis of studies examining the influence of concomitant PSC on colorectal cancer risk in IBD strongly suggested that PSC is independently associated with cancer risk [79]. The risk of colorectal cancer appears to vary significantly across study populations. A recently published population-based study from a Hungarian province noted a cumulative risk of colorectal cancer of 9% at 20 years and 13% at 30 years [80]. The natural history of IBD and its complications are perhaps best characterized in population-based incidence cohorts of UC and Crohn's disease from Copenhagen County, Denmark. Surprisingly, the absolute and relative risk of colorectal cancer in these cohorts has been low by historical standards [81,82]. Additional follow-up of the Copenhagen County cohorts with respect to cancer risk has been published recently [83•,84]. Whereas the risk of small bowel adenocarcinoma was over 60 times higher than expected in Crohn's disease, the risk of colorectal cancer was not significantly elevated in either IBD subtype [83•,84]. The authors attributed this low risk to a high prevalence of 5-aminosalicylate use and an aggressive surgical treatment strategy, but this remains speculative.

A widely adopted strategy to manage the risk of colorectal dysplasia and cancer has been surveillance colonoscopy with biopsy. This approach is not ideal for several reasons, including sampling error and the poor interobserver variability of histologic findings, such as low-grade dysplasia. Other detection techniques and markers for neoplasia risk in this setting are being investigated. A study from the University of Washington described a polymerase chain reaction–based method of "DNA fingerprinting" that revealed differences in genomic stability between UC patients with and without colorectal dysplasia or cancer [85]. A retrospective cohort study of immunohistochemical staining for abnormal p53 in patients with UC-related colorectal cancer showed a higher mortality rate in patients who had tumors with positive staining [86]. However, at this point evidence is not sufficient to recommend the routine use of these techniques in surveillance. A particularly promising technique for neoplasia identification during surveillance is chromoendoscopy [87•]. One hundred sixty-five German UC patients were randomly assigned to conventional surveillance colonoscopy or methylene blue–aided chromoendoscopy using a high-magnification scope, and the detection rate for dysplasia in the latter group was triple that of the former [87•]. A similar prospective trial in over 300 British patients, comparing conventional surveillance to indigo carmine–aided chromoendoscopy, produced similarly impressive results [88].

The management of low-grade dysplasia in UC continues to be controversial. A study from Mount Sinai Medical Center (New York) identified a retrospective cohort of 46 patients with low-grade dysplasia [89•]. Seven of these patients developed colorectal cancer, most with stage II or higher disease. Unexpected advanced neoplasia (high-grade dysplasia or cancer) was identified in approximately one quarter of those who went to colectomy. The actuarial rate of progression to high-grade dysplasia or cancer was 53% at 5 years from the initial finding of low-grade dysplasia [89•]. This progression rate is similar to that noted elsewhere [90].

Colorectal cancer chemoprevention in IBD is of great interest. Several observational studies from the past 18 months have suggested that regular use of 5-aminosalicylate agents such as sulfasalazine and mesalamine are inversely associated with IBD-related cancer or dysplasia [91,92•], but

data are conflicting [93,94]. A meta-analysis of all observational studies on this topic was preliminarily reported and suggested that regular use of aminosalicylates was indeed protective [95•]. More robust studies, preferably larger and/or prospective, are likely needed to prove this effect. Patients with concomitant IBD who had been enrolled in a randomized clinical trial of ursodeoxycholic acid (UDCA) for PSC were studied for the subsequent development of colorectal dysplasia or cancer [96•]. The cumulative incidence of colorectal neoplasia was 10% in the UDCA-treated patients versus 35% in the placebo-treated patients. The relative risk of colorectal neoplasia was significantly lower in the UDCA-treated patients (RR=0.26) [96•].

Conclusions

Data on the prevalence, risk factors, and pathogenesis of extraintestinal manifestations of IBD continue to accumulate. Great strides in the medical management of many but not all of these complications have been made, especially with the advent of biologic therapies. The detection and management of colorectal neoplasia in IBD continues to be troublesome, although there is promise that strategies to prevent the development of this feared complication can be found.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Orchard TR, Chua CN, Ahmad T, *et al.*: **Uveitis and erythema nodosum in inflammatory bowel disease: clinical features and the role of HLA genes.** *Gastroenterology* 2002, **123:**714–718.

2.• Ricart E, Panaccione R, Loftus EV, *et al.*: **Autoimmune disorders and extraintestinal manifestations in first-degree familial and sporadic inflammatory bowel disease: a case-control study.** *Inflamm Bowel Dis* 2004, **10:**207–14.

Comparison of the prevalence of EIMs and autoimmune diseases among sporadic IBD and familial IBD patients and their relatives.

3.• Manguso F, Sanges M, Staiano T, *et al.*: **Cigarette smoking and appendectomy are risk factors for extraintestinal manifestations in ulcerative colitis.** *Am J Gastroenterol* 2004, **99:**327–334.

Cigarette smoking and appendectomy may increase the risk of certain EIMs in patients with IBD.

4. Salvarani C, Vlachonikolis IG, van der Heijde DM, *et al.*, and the European Collaborative for IBDSG: **Musculoskeletal manifestations in a population-based cohort of inflammatory bowel disease patients.** *Scand J Gastroenterol* 2001, **36:**1307–1313.

5. Bernstein CN, Blanchard JF, Rawsthorne P, Yu N: **The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study.** *Am J Gastroenterol* 2001, **96:**1116–1122.

6. Palm O, Moum B, Ongre A, Gran JT: **Prevalence of ankylosing spondylitis and other spondyloarthropathies among patients with inflammatory bowel disease: a population study (the IBSEN study).** *J Rheumatol* 2002, **29:**511–515.

7. Steer S, Jones H, Hibbert J, *et al.*: **Low back pain, sacroiliitis, and the relationship with HLA-B27 in Crohn's disease.** *J Rheumatol* 2003, **30:**518–522.

8. Mielants H, Veys E, Cuvelier C, De Vos M: **HLA B27 related arthritis and bowel inflammation. II. Ileocolonoscopy and bowel histology in patients with HLA B27 related arthritis.** *J Rheumatol* 1985, **12:**294–298.

9. De Vos M, Mielants H, Cuvelier C, *et al.*: **Long-term evolution of gut inflammation in patients with spondyloarthropathy.** *Gastroenterology* 1996, **110:**1696–1703.

10. Bjarnason I, Helgason KO, Geirsson AJ, *et al.*: **Subclinical intestinal inflammation and sacroiliac changes in relatives of patients with ankylosing spondylitis.** *Gastroenterology* 2003, **125:**1598–1605.

11. Hoffman IE, Demetter P, Peeters M, *et al.*: **Anti-saccharomyces cerevisiae IgA antibodies are raised in ankylosing spondylitis and undifferentiated spondyloarthropathy.** *Ann Rheum Dis* 2003, **62:**455–459.

12. Miceli-Richard C, Zouali H, Lesage S, *et al.*: **CARD15/NOD2 analyses in spondylarthropathy.** *Arthritis Rheum* 2002, **46:**1405–1406.

13. Ferreiros-Vidal I, Amarelo J, Barros F, *et al.*: **Lack of association of ankylosing spondylitis with the most common NOD2 susceptibility alleles to Crohn's disease.** *J Rheumatol* 2003, **30:**102–104.

14. van der Paardt M, Crusius JB, de Koning MH, *et al.*: **CARD15 gene mutations are not associated with ankylosing spondylitis.** *Genes Immun* 2003, **4:**77–78.

15. De Vos M, Laukens D, Marichal D, *et al.*: **CARD15 mutations in patients with spondyloarthropathy are linked with disease progression and evolution to Crohn's disease [abstract].** *Gastroenterology* 2003, **124:**A48.

16. Braun J, Brandt J, Listing J, *et al.*: **Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial.** *Lancet* 2002, **359:**1187–1193.

17. Braun J, Brandt J, Listing J, *et al.*: **Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebo-controlled trial.** *Arthritis Rheum* 2003, **48:**2224–2233.

18. Gorman JD, Sack KE, Davis JC Jr: **Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha.** *N Engl J Med* 2002, **346:**1349–1356.

19. Brandt J, Khariouzov A, Listing J, *et al.*: **Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis.** *Arthritis Rheum* 2003, **48:**1667–1675.

20. Davis JC Jr, Van Der Heijde D, Braun J, *et al.*, and the Ankylosing Spondylitis Study Group. **Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial.** *Arthritis Rheum* 2003, **48:**3230–3236.

21.• Maksymowych WP, Inman RD, Gladman D, *et al.*, and the Spondyloarthritis Research Consortium of Canada (SPARCC): **Canadian Rheumatology Association Consensus on the use of anti-tumor necrosis factor-alpha directed therapies in the treatment of spondyloarthritis.** *J Rheumatol* 2003, **30:**1356–1363.

Consensus statement from a national rheumatologic society outlining indications for anti-TNF therapy in spondyloarthropathy.

22. Palm O, Moum B, Jahnsen J, Gran JT: **The prevalence and incidence of peripheral arthritis in patients with inflammatory bowel disease, a prospective population-based study (the IBSEN study).** *Rheumatology* 2001, **40:**1256–1261.

23. Orchard TR, Wordsworth BP, Jewell DP: **Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history.** *Gut* 1998, **42:**387–391.

24. Orchard TR, Thiyagaraja S, Welsh KI, *et al.*: **Clinical phenotype is related to HLA genotype in the peripheral arthropathies of inflammatory bowel disease.** *Gastroenterology* 2000, **118:**274–278.

25. Balbir-Gurman A, Schapira D, Nahir M: **Arthritis related to ileal pouchitis following total proctocolectomy for ulcerative colitis.** *Semin Arthritis Rheum* 2001, **30:**242–248.

26.• Reinisch W, Miehsler W, Dejaco C, *et al.*: **An open-label trial of the selective cyclo-oxygenase-2 inhibitor, rofecoxib, in inflammatory bowel disease-associated peripheral arthritis and arthralgia.** *Aliment Pharmacol Ther* 2003, **17:**1371–1380.
An uncontrolled study suggesting that rofecoxib does not significantly increase the risk of disease exacerbation in IBD.

27. Mahadevan U, Loftus EV Jr, Tremaine WJ, Sandborn WJ: **Safety of selective cyclooxygenase-2 inhibitors in inflammatory bowel disease.** *Am J Gastroenterol* 2002, **97:**910–914.

28. Menachem Y, Gotsman I: **Clinical manifestations of pyoderma gangrenosum associated with inflammatory bowel disease.** *Isr Med Assoc J* 2004, **6:**88–90.

29. Newman B, Cescon D, Domenchini A, Siminovitch KA: **CD2BP1 and CARD15 mutations are not associated with pyoderma gangrenosum in patients with inflammatory bowel disease.** *J Invest Dermatol* 2004, **122:**1054–1056.

30. Vidal D, Alomar A: **Successful treatment of periostomal pyoderma gangrenosum using topical tacrolimus.** *Br J Dermatol* 2004, **150:**387–388.

31. Ljung T, Staun M, Grove O, *et al.*: **Pyoderma gangrenosum associated with Crohn disease: effect of TNF-alpha blockade with infliximab.** *Scand J Gastroenterol* 2002, **37:**1108–1110.

32. Kugathasan S, Miranda A, Nocton J, *et al.*: **Dermatologic manifestations of Crohn disease in children: response to infliximab.** *J Pediatr Gastroenterol Nutr* 2003, **37:**150–154.

33.• Regueiro M, Valentine J, Plevy S, *et al.*: **Infliximab for treatment of pyoderma gangrenosum associated with inflammatory bowel disease.** *Am J Gastroenterol* 2003, **98:**1821–1826.
Case series demonstrating the effectiveness of infliximab in refractory pyoderma gangrenosum.

34. Mintz R, Feller ER, Bahr RL, Shah SA: **Ocular manifestations of inflammatory bowel disease.** *Inflamm Bowel Dis* 2004, **10:**135–139.

35. Munoz-Fernandez S, Hidalgo V, Fernandez-Melon J, *et al.*: **Sulfasalazine reduces the number of flares of acute anterior uveitis over a one-year period.** *J Rheumatol* 2003, **30:**1277–1279.

36. Kaplan-Messas A, Barkana Y, Avni I, Neumann R: **Methotrexate as a first-line corticosteroid-sparing therapy in a cohort of uveitis and scleritis.** *Ocular Immunol Inflamm* 2003, **11:**131–139.

37. Baltatzis S, Tufail F, Yu EN, *et al.*: **Mycophenolate mofetil as an immunomodulatory agent in the treatment of chronic ocular inflammatory disorders.** *Ophthalmology* 2003, **110:**1061–1065.

38. Lau CH, Comer M, Lightman S: **Long-term efficacy of mycophenolate mofetil in the control of severe intraocular inflammation.** *Clin Exp Ophthalmol* 2003, **31:**487–491.

39. Joseph A, Raj D, Dua HS, *et al.*: **Infliximab in the treatment of refractory posterior uveitis.** *Ophthalmology* 2003, **110:**1449–1453.

40. Murphy CC, Ayliffe WH, Booth A, *et al.*: **Tumor necrosis factor alpha blockade with infliximab for refractory uveitis and scleritis.** *Ophthalmology* 2004, **111:**352–356.

41. Reiff A: **Long-term outcome of etanercept therapy in children with treatment-refractory uveitis.** *Arthritis Rheum* 2003, **48:**2079–2080.

42. Foster CS, Tufail F, Waheed NK, *et al.*: **Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate.** *Arch Ophthalmol* 2003, **121:**437–440.

43. Murphy CC, Greiner K, Plskova J, *et al.*: **Neutralizing tumor necrosis factor activity leads to remission in patients with refractory noninfectious posterior uveitis.** *Arch Ophthalmol* 2004, **122:**845–851.

44. Nussenblatt RB, Thompson DJ, Li Z, *et al.*: **Humanized anti-interleukin-2 (IL-2) receptor alpha therapy: long-term results in uveitis patients and preliminary safety and activity data for establishing parameters for subcutaneous administration.** *J Autoimmun* 2003, **21:**283–293.

45. Papaliodis GN, Chu D, Foster CS: **Treatment of ocular inflammatory disorders with daclizumab.** *Ophthalmology* 2003, **110:**786–789.

46.• Bambha K, Kim WR, Talwalkar J, *et al.*: **Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a United States community.** *Gastroenterology* 2003, **125:**1364–1369.
First population-based study of the incidence and clinical features of PSC from a region in the United States.

47. Florin TH, Pandeya N, Radford-Smith GL: **Epidemiology of appendicectomy in primary sclerosing cholangitis and ulcerative colitis: its influence on the clinical behaviour of these diseases.** *Gut* 2004, **53:**973–979.

48. Perdigoto R, Wiesner RH, LaRusso NF, Dozois R: **Inflammatory bowel disease associated with primary sclerosing cholangitis: incidence, severity and relationship to liver disease [abstract].** *Gastroenterology* 1991, **100:**A238.

49. Harewood GC, Loftus EV, Tremaine WJ, Sandborn WJ: **'PSC-IBD': a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis [abstract].** *Gastroenterology* 1999, **116:**A732.

50.• Loftus EV, Harewood GC, Loftus CG, *et al.*: **PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis.** *Gut* 2004, in press.
Comparison of the colonoscopic features of PSC-associated IBD with UC, demonstrating that rectal sparing and backwash ileitis are more common in PSC–IBD.

51. Boberg KM, Egeland T, Schrumpf E: **Long-term effect of corticosteroid treatment in primary sclerosing cholangitis patients.** *Scand J Gastroenterol* 2003, **38:**991–995.

52. Epstein MP, Kaplan MM: **A pilot study of etanercept in the treatment of primary sclerosing cholangitis.** *Dig Dis Sci* 2004, **49:**1–4.

53. Haagsma EB, Van Den Berg AP, Kleibeuker JH, *et al.*: **Inflammatory bowel disease after liver transplantation: the effect of different immunosuppressive regimens.** *Aliment Pharmacol Ther* 2003, **18:**33–44.

54. Vera A, Gunson BK, Ussatoff V, *et al.*: **Colorectal cancer in patients with inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis.** *Transplantation* 2003, **75:**1983–1988.

55.• Bernstein CN, Leslie WD, Leboff MS: **AGA technical review on osteoporosis in gastrointestinal diseases.** *Gastroenterology* 2003, **124:**795–841.
Comprehensive review of IBD-associated osteoporosis that served as a basis for AGA practice guidelines.

56. **American Gastroenterological Association medical position statement: guidelines on osteoporosis in gastrointestinal diseases.** *Gastroenterology* 2003, **124:**791–794.

57. Bernstein CN, Katz S: *Osteoporosis and Inflammatory Bowel Disease: A Guide to Diagnosis and Management for the Gastroenterologist.* Arlington, VA: American College of Gastroenterology; 2002.

58. Jahnsen J, Falch JA, Mowinckel P, Aadland E: **Bone mineral density in patients with inflammatory bowel disease: a population-based prospective two-year follow-up study.** *Scand J Gastroenterol* 2004, **39:**145–153.

59. Hanley DA, Brown JP, Tenenhouse A, *et al.*, and the Canadian Multicentre Osteoporosis Study Research Group: **Associations among disease conditions, bone mineral density, and prevalent vertebral deformities in men and women 50 years of age and older: cross-sectional results from the Canadian Multicentre Osteoporosis Study.** *J Bone Miner Res* 2003, **18:**784–790.

60. de Jong DJ, Mannaerts L, van Rossum LG, *et al.*: **Longitudinal study of bone mineral density in patients with Crohn's disease.** *Dig Dis Sci* 2003, **48:**1355–1359.

61. Bernstein CN, Leslie WD, Taback SP: **Bone density in a population-based cohort of premenopausal adult women with early onset inflammatory bowel disease.** *Am J Gastroenterol* 2003, **98:**1094–1100.

62. Bernstein CN, Bector S, Leslie WD: **Lack of relationship of calcium and vitamin D intake to bone mineral density in premenopausal women with inflammatory bowel disease.** *Am J Gastroenterol* 2003, **98:**2468–2473.

63. Siffledeen JS, Siminoski K, Steinhart H, *et al.*: **The frequency of vitamin D deficiency in adults with Crohn's disease.** *Can J Gastroenterol* 2003, **17:**473–478.

64. Bernstein CN, Blanchard JF, Leslie W, *et al.*: **The incidence of fracture among patients with inflammatory bowel disease: a population-based cohort study.** *Ann Intern Med* 2000, **133:**795–799.
65. Vestergaard P, Mosekilde L: **Fracture risk in patients with celiac disease, Crohn's disease, and ulcerative colitis: a nationwide follow-up study of 16,416 patients in Denmark.** *Am J Epidemiol* 2002, **156:**1–10.
66. Loftus EV Jr, Crowson CS, Sandborn WJ, *et al.*: **Long-term fracture risk in patients with Crohn's disease: a population-based study in Olmsted County, Minnesota.** *Gastroenterology* 2002, **123:**468–475.
67. Loftus EV Jr, Achenbach SJ, Sandborn WJ, *et al.*: **Risk of fracture in ulcerative colitis: a population-based study from Olmsted County, Minnesota.** *Clin Gastroenterol Hepatol* 2003, **1:**465–473.
68.• van Staa TP, Cooper C, Brusse LS, *et al.*: **Inflammatory bowel disease and the risk of fracture.** *Gastroenterology* 2003, **125:**1591–1597.
Large case–control study from the GPRD demonstrating a relationship between hip and vertebral fractures and IBD.
69.• Card T, West J, Hubbard R, Logan RF: **Hip fractures in patients with inflammatory bowel disease and their relationship to corticosteroid use: a population based cohort study.** *Gut* 2004, **53:**251–255.
Large matched cohort study, also from the GPRD, demonstrating an increased risk of hip fracture in Crohn's disease and UC. This study also suggests that corticosteroid use further increased the risk of fracture.
70. Bernstein CN, Blanchard JF, Metge C, Yogendran M: **The association between corticosteroid use and development of fractures among IBD patients in a population-based database.** *Am J Gastroenterol* 2003, **98:**1797–1801.
71. Bartram SA, Peaston RT, Rawlings DJ, *et al.*: **A randomized controlled trial of calcium with vitamin D, alone or in combination with intravenous pamidronate, for the treatment of low bone mineral density associated with Crohn's disease.** *Aliment Pharmacol Ther* 2003, **18:**1121–1127.
72. von Tirpitz C, Klaus J, Steinkamp M, *et al.*: **Therapy of osteoporosis in patients with Crohn's disease: a randomized study comparing sodium fluoride and ibandronate.** *Aliment Pharmacol Ther* 2003, **17:**807–816.
73. Papa A, Danese S, Grillo A, *et al.*: **Review article: Inherited thrombophilia in inflammatory bowel disease.** *Am J Gastroenterol* 2003, **98:**1247–1251.
74. Bernstein CN, Blanchard JF, Houston DS, Wajda A: **The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study.** *Thromb Haemost* 2001, **85:**430–434.
75.• Miehsler W, Reinisch W, Valic E, *et al.*: **Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism?** *Gut* 2004, **53:**542–548.
IBD appears to be a risk factor for thromboembolism, whereas rheumatoid arthritis and celiac disease do not.
76. Solem CA, Loftus EV, Tremaine WJ, Sandborn WJ: **Venous thromboembolism in inflammatory bowel disease.** *Am J Gastroenterol* 2004, **99:**97–101.
77. Papa A, Danese S, Piccirillo N, *et al.*: **Thrombopoietin serum levels in patients with inflammatory bowel disease with and without previous thromboembolic events.** *Hepatogastroenterology* 2003, **50:**132–135.
78. Eaden JA, Abrams KR, Mayberry JF: **The risk of colorectal cancer in ulcerative colitis: a meta-analysis.** *Gut* 2001, **48:**526–535.
79. Soetikno RM, Lin OS, Heidenreich PA, *et al.*: **Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis.** *Gastrointest Endosc* 2002, **56:**48–54.
80. Lakatos L, Mester G, Erdelyi Z, *et al.*: **Striking elevation in incidence and prevalence of inflammatory bowel disease in a province of western Hungary between 1977-2001.** *World J Gastroenterol* 2004, **10:**404–409.
81. Langholz E, Munkholm P, Davidsen M, Binder V: **Colorectal cancer risk and mortality in patients with ulcerative colitis.** *Gastroenterology* 1992, **103:**1444–1451.
82. Munkholm P, Langholz E, Davidsen M, Binder V: **Intestinal cancer risk and mortality in patients with Crohn's disease.** *Gastroenterology* 1993, **105:**1716–1723.
83.• Jess T, Winther KV, Munkholm P, *et al.*: **Intestinal and extra-intestinal cancer in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark.** *Aliment Pharmacol Ther* 2004, **19:**287–293.
Population-based study from Copenhagen County, Denmark demonstrating an elevated risk of small bowel cancer, but not colorectal cancer, in an incidence cohort of Crohn's disease.
84. Winther KV, Jess T, Langholz E, *et al.*: **Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County.** *Clin Gastroenterol Hepatol* 2004, in press.
85. Chen R, Rabinovitch PS, Crispin DA, *et al.*: **DNA fingerprinting abnormalities can distinguish ulcerative colitis patients with dysplasia and cancer from those who are dysplasia/cancer-free.** *Am J Pathol* 2003, **162:**665–672.
86. Lashner BA, Bauer WM, Rybicki LA, Goldblum JR: **Abnormal p53 immunohistochemistry is associated with an increased colorectal cancer-related mortality in patients with ulcerative colitis.** *Am J Gastroenterol* 2003, **98:**1423–1427.
87.• Kiesslich R, Fritsch J, Holtmann M, *et al.*: **Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis.** *Gastroenterology* 2003, **124:**880–888.
In a randomized prospective study, this promising technique detected three times as many dysplastic lesions as did conventional surveillance colonoscopy.
88. Hurlstone DP, McAlindon ME, Sanders DS, *et al.*: **Further validation of high-magnification chromoscopic-colonoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis.** *Gastroenterology* 2004, **126:**376–378.
89.• Ullman T, Croog V, Harpaz N, *et al.*: **Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis.** *Gastroenterology* 2003, **125:**1311–1319.
The actuarial progression rate of low-grade dysplasia to either high-grade dysplasia or cancer was over 50% after 5 years.
90. Ullman TA, Loftus EV Jr, Kakar S, *et al.*: **The fate of low grade dysplasia in ulcerative colitis.** *Am J Gastroenterol* 2002, **97:**922–927.
91. Rubin DT, Djordjevic A, Huo D, *et al.*: **Use of 5-ASA is associated with decreased risk of dysplasia and colon cancer in ulcerative colitis [abstract].** *Gastroenterology* 2003, **124:**A36.
92.• van Staa TP, Card T, Leufkens HGM, Logan RF: **Prior aminosalicylate use and the development of colorectal cancer in inflammatory bowel disease (IBD): a large British epidemiological study [abstract].** *Am J Gastroenterol* 2003, **98:**S244–S245.
In this nested case–control study from the GPRD, regular users of 5-aminosalicylate agents were approximately 30% to 40% less likely to develop colorectal cancer than were irregular users.
93. Bernstein CN, Blanchard JF, Metge C, Yogendran M: **Does the use of 5-aminosalicylates in inflammatory bowel disease prevent the development of colorectal cancer?** *Am J Gastroenterol* 2003, **98:**2784–2788.
94. Rutter M, Saunders B, Wilkinson K, *et al.*: **Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis.** *Gastroenterology* 2004, **126:**451–459.
95.• Velayos FS, Walsh JME, Terdiman JP: **Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk in ulcerative colitis: a meta-analysis [abstract].** *Gastroenterology* 2004, **126:**A20.
Meta-analysis of the observational studies on 5-aminosalicylate and colorectal neoplasia. Pooling of the data suggested a cancer risk reduction of 75%.
96.• Pardi DS, Loftus EV Jr, Kremers WK, *et al.*: **Ursodeoxycholic acid as a chemopreventive agent in patients with ulcerative colitis and primary sclerosing cholangitis.** *Gastroenterology* 2003, **124:**889–893.
PSC–IBD patients who received UCDA in a randomized trial were 74% less likely than those receiving placebo to develop colorectal dysplasia or cancer.