

# Extraintestinal Manifestations of Inflammatory Bowel Disease

Stephan R. Vavricka, MD,<sup>\*,†</sup> Alain Schoepfer, MD,<sup>‡</sup> Michael Scharl, MD,<sup>\*</sup> Peter L. Lakatos, MD,<sup>§</sup> Alexander Navarini, MD,<sup>||</sup> and Gerhard Rogler, MD<sup>\*</sup>

**Abstract:** Extraintestinal manifestations (EIM) in inflammatory bowel disease (IBD) are frequent and may occur before or after IBD diagnosis. EIM may impact the quality of life for patients with IBD significantly requiring specific treatment depending on the affected organ(s). They most frequently affect joints, skin, or eyes, but can also less frequently involve other organs such as liver, lungs, or pancreas. Certain EIM, such as peripheral arthritis, oral aphthous ulcers, episcleritis, or erythema nodosum, are frequently associated with active intestinal inflammation and usually improve by treatment of the intestinal activity. Other EIM, such as uveitis or ankylosing spondylitis, usually occur independent of intestinal inflammatory activity. For other not so rare EIM, such as pyoderma gangrenosum and primary sclerosing cholangitis, the association with the activity of the underlying IBD is unclear. Successful therapy of EIM is essential for improving quality of life of patients with IBD. Besides other options, tumor necrosis factor antibody therapy is an important therapy for EIM in patients with IBD.

(*Inflamm Bowel Dis* 2015;21:1982–1992)

**Key Words:** extraintestinal manifestations, inflammatory bowel disease, arthritis, uveitis

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), should be regarded as a systemic disorder not limited to the gastrointestinal tract because many patients will develop extraintestinal symptoms. Extraintestinal symptoms may involve virtually any organ system with a potentially detrimental impact on the patient's functional status and quality of life.

Extraintestinal symptoms can be divided in 2 groups: extraintestinal manifestations (EIM) and extraintestinal complications. EIM most frequently affect joints (peripheral and axial arthropathies), the skin (erythema nodosum, pyoderma gangrenosum, Sweet's syndrome, aphthous stomatitis), the hepatobiliary tract (primary sclerosing cholangitis [PSC]), and the eye (episcleritis, uveitis) (Fig. 1). Less frequently, EIM also affect the lungs, the heart, the pancreas, or the

vascular system. Extraintestinal complications are mainly caused by the disease itself and include conditions such as malabsorption with consequent micronutrient deficiencies, osteoporosis, peripheral neuropathies, kidney stones, gallstones, and IBD drug-related side effects.

This article focuses on the clinical features of EIM. Certain EIM such as pauciarticular arthritis, oral aphthous ulcers, erythema nodosum, or episcleritis usually occur with increased intestinal disease activity.<sup>1,2</sup> Other EIM such as ankylosing spondylitis and uveitis usually follow an independent course from IBD disease activity.<sup>1,2</sup> And finally, some EIM such as PSC and pyoderma gangrenosum may or may not be related to IBD disease activity (Table 1).<sup>2–4</sup>

EIM in IBD are reported with frequencies ranging from 6% to 47%.<sup>5–13</sup> Multiple EIM may occur concomitantly, and the presence of 1 EIM confers a higher likelihood to develop other EIM.<sup>14</sup> Recently, we reported based on data from the Swiss IBD Cohort study that up to 1 quarter of EIM-affected patients with IBD tend to suffer from a combination of several EIMs (up to 5).<sup>14</sup> Furthermore, our group recently published data regarding the chronological order of EIM appearance relative to IBD diagnosis.<sup>15</sup> A summary of the chronologic appearance of EIMs relative to IBD diagnosis is presented in Figure 2. In 25.8% of cases, a first EIM occurred before IBD was diagnosed (median time 5 mo before IBD diagnosis; range, 0–25 mo). In 74.2% of cases, the first EIM manifested after IBD diagnosis was made (median, 92 mo; range, 29–183 mo) (Fig. 2). We found that up to 4 different EIM occurred before IBD was diagnosed, and that at 30 years after IBD diagnosis, 50% of patients had suffered from at least 1 EIM. Perianal CD, colonic involvement, and cigarette smoking increased the likelihood to suffer from EIMs.<sup>16</sup>

## PATHOGENESIS OF EIM

The pathogenesis of EIM in IBD is not well understood. It is believed that the diseased gastrointestinal mucosa may trigger

Received for publication November 6, 2014; Accepted February 9, 2015.

From the \*Department of Medicine, Division of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland; †Department of Medicine, Division of Gastroenterology and Hepatology, Triemli Hospital Zurich, Zurich, Switzerland; ‡Department of Medicine, Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; §1st Department of Medicine, Semmelweis University, Budapest, Hungary; and ||Department of Dermatology, University Hospital Zurich, Zurich, Switzerland.

Supported by research grants from the Swiss National Science Foundation (33CSCO\_134274 [Swiss IBD Cohort Study] to G. Rogler, 320000-114009/3 and 32473B\_135694/1 to S. R. Vavricka, and 314730-146204 and CRSII3\_154488/1 to M. Scharl) and the Zurich Center for Integrative Human Physiology of the University of Zurich (to G. Rogler, M. Scharl, and S. R. Vavricka).

The authors have no conflicts of interest to disclose.

Reprints: Stephan R. Vavricka, MD, Department of Internal Medicine, Division of Gastroenterology, Triemli Hospital, Birmensdorfstrasse 497, CH-8063 Zurich, Switzerland (e-mail: stephan.vavricka@usz.ch).

Copyright © 2015 Crohn's & Colitis Foundation of America, Inc. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

DOI 10.1097/MIB.0000000000000392

Published online 2 July 2015.

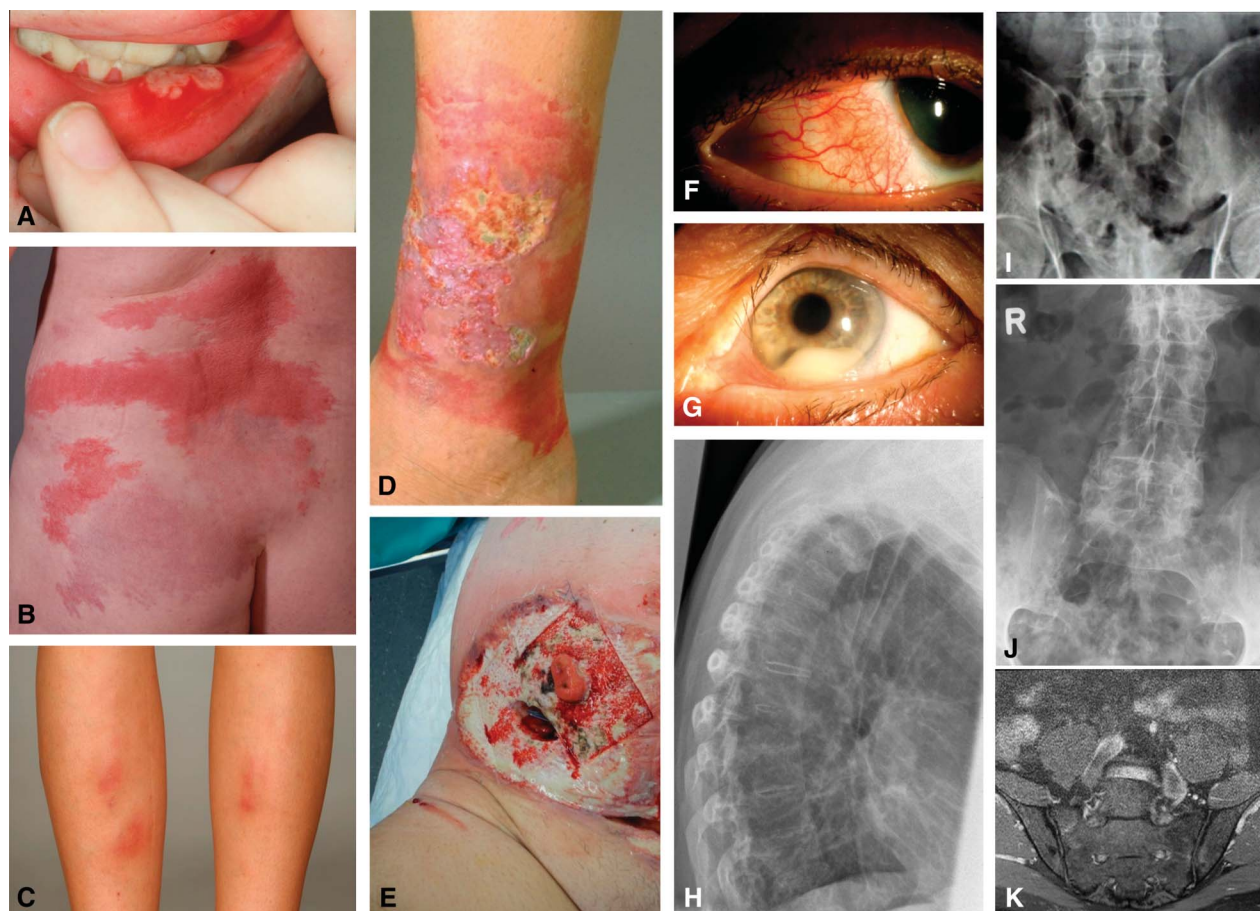


FIGURE 1. A, Oral aphthous ulcers, (B) Sweet's syndrome, (C) erythema nodosum, (D) pyoderma gangrenosum, (E) peristomal pyoderma gangrenosum, (F) episcleritis, (G) uveitis with hypopyon and dilated iris vessels, (H) conventional x-ray of the lateral spine demonstrating syndesmophytes (bamboo spine), (I) plane radiograph of the ileosacral joints with bilateral sacroiliitis, (J) plane radiography of the sacrum with bilateral ankylosis, (K) coronal magnetic resonance image of the sacroiliac joints with active inflammation mainly on the left side and chronic inflammatory changes on both sides.

immune responses at the extraintestinal site due to shared epitopes, e.g., of intestinal bacteria and the synovia.<sup>17–21</sup> This would mean that bacteria that are translocated across the leaky intestinal barrier trigger an adaptive immune response that finally is unable to discriminate between bacterial epitopes and epitopes of joints or the skin. Triggers of the autoimmune responses in certain organs seem to be influenced by genetic factors. Concordance in EIM was present in 70% of parent–child pairs and 84% in sibling pairs.<sup>10,22</sup> Associations of EIM in IBD with major histocompatibility complex loci have been demonstrated. EIM in patients with CD are more frequently observed in patients with HLA-A2, HLA-DR1, and HLA-DQw5, whereas EIM in patients with UC are more likely to appear when the HLA-DR103 genotype is present.<sup>23</sup> Particular HLA complexes have also been linked to specific EIM. HLA-B8/DR3 is associated with an increased risk of PSC in UC, whereas HLA-DRB1\*0103, HLA-B\*27, and HLA-B\*58 are associated with EIM of joints, the skin, and eyes, respectively, in patients with IBD.<sup>4,24,25</sup> HLA-B\*27 itself does not seem to be associated with IBD<sup>5</sup> but HLA-B\*27 shows

a strong association with the development of ankylosing spondylitis, as 50% to 90% of patients with IBD are positive for this marker.<sup>26</sup> As HLA-B\*27 per se shows an association with ankylosing spondylitis or rheumatoid arthritis it remains unclear whether there is a specific role for EIM in IBD.

## MUSCULOSKELETAL EIM

Musculoskeletal EIM including joint complaints represent the most common EIMs in IBD. Joint symptoms affecting peripheral large and small joints or the axial joints occur in up to 40% of patients with IBD.<sup>14,27,28</sup>

### Peripheral Arthralgia/Arthritis

Peripheral arthralgia/arthritis in patients with IBD, in contrast to other specific forms of arthritis such as rheumatoid arthritis or psoriatic arthritis, shows little or no joint destruction. Classically, it presents as a seronegative arthralgia/arthritis,<sup>1</sup> which affects 5% to 10% of patients with UC and 10% to 20%

**TABLE 1.** Relationship Between EIM Activity and Intestinal Activity

EIM	Parallel Course of IBD	Separate Course of IBD	May or May Not Parallel Disease Activity
Axial arthropathy		✓	
Peripheral arthropathy	✓ (Type I)	✓ (Type II)	
Erythema nodosum	✓		
Pyoderma gangrenosum			✓
Sweet's syndrome	✓		
Oral aphthous ulcers	✓		
Episcleritis	✓		
Uveitis			✓
PSC			✓

Adapted from Trikudanathan et al.<sup>2</sup>

of patients with CD.<sup>29</sup> A higher risk for peripheral arthralgia/arthritis is seen in patients with IBD with colonic involvement and in patients suffering from perianal disease, erythema nodosum, stomatitis, uveitis, and pyoderma gangrenosum.<sup>1,20</sup>

Peripheral arthralgia/arthritis has been classified into 2 entities (Table 2): type I (pauciarticular) arthralgia/arthritis usually affects less than 5 large joints, such as ankles, knees, hips, wrists, elbows, and shoulders and is often acute, asymmetrical, and migratory. The knee is commonly involved. Approximately, 20% to 40% of all patients have more than 1 episode of arthralgia/arthritis. Pauciarticular arthralgia/arthritis is usually related to IBD activity and self-limiting with a maximum duration of up to 10 weeks.<sup>29</sup> Consequently, medical or surgical treatment of the underlying intestinal inflammation (i.e., colitis) is usually associated with improvement of type I arthritis. Type II (polyarticular)

**TABLE 2.** Classification of Peripheral Arthropathy Associated with IBD

Type 1 (Pauciarticular)	Type 2 (Polyarticular)
Prevalence in UC, 35%	Prevalence in UC, 24%
Prevalence in CD, 29%	Prevalence in CD, 20%
Less than 5 joints	Five or more joints
Mainly large joints	Mainly small joints
Knee > ankle > wrist > elbow > MCP > hip > shoulder	MCP > knees > PIP > wrist > ankle > elbow > shoulder
Asymmetric involvement	It can be symmetric or asymmetric, may be erosive
Parallels intestinal disease activity	Clinical course independent of IBD activity
Self-limited episodes that last <10 wk	Persistent inflammation for months or even years
High frequency of other EIM (erythema nodosum and uveitis)	Associated only with uveitis
Associated with HLA-B27, B35, and DR103	Associated with HLA-B44

PIP, proximal interphalangeal joint; MCP, metacarpophalangeal joint.

Combined use of the Assessment of SpondyloArthritis International Society (ASAS) criteria for axial spondyloarthritis (SpA) and the ASAS criteria for peripheral SpA in the entire SpA population. In patients with predominantly axial involvement (back pain) with or without peripheral manifestations, the ASAS criteria for axial SpA6 are applied. In patients with peripheral manifestations only, the ASAS criteria for peripheral SpA are applied. In the entire ASAS population of 975 patients' sensitivity and specificity of the combined use of the 2 sets of criteria were 79.5% and 83.3%, respectively.

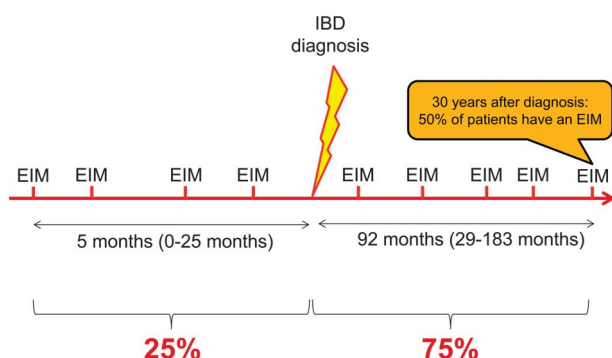
Adapted from Su et al,<sup>10</sup> Orchard et al,<sup>29</sup> and Rodriguez-Reyna et al.<sup>30</sup>

arthralgia/arthritis frequently is a symmetrical arthritis involving 5 or more small joints. It is not related with intestinal disease activity and may precede IBD diagnosis. Type II arthropathy can persist for years (median of 3 yr).<sup>29</sup> The metacarpophalangeal joint is most commonly involved. Type II arthritis is associated with an increased risk of uveitis but not erythema nodosum.<sup>29</sup>

The diagnosis/classification of type 1 and type 2 arthropathies is purely clinical, as imaging is most often normal with no evidence of significant inflammation or joint destruction.<sup>31</sup> Both types are seronegative (i.e., rheumatoid factor-negative), but may represent immunogenetically distinct entities. Type 1 peripheral arthropathy is associated with HLA-B27, HLA-B35, and HLA-DR103, whereas type 2 is associated with HLA-B44.<sup>25</sup>

As type II peripheral arthropathy usually occurs independently from intestinal activity and anti-inflammatory treatment may not be successful, physiotherapy and treatment of associated pain is the main treatment option in those cases.

Table 3 summarizes treatment options of EIM in IBD. Other treatment modalities include rest, and intra-articular steroid injections. Use of sulphasalazine has been reported to improve peripheral arthropathies.<sup>45</sup> Therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) in the management of IBD-associated peripheral arthropathies requires caution



**FIGURE 2.** Chronology of EIM in patients with IBD. In one quarter of patients with IBD, up to 4 EIM appeared before the time of IBD diagnosis. The median time before IBD diagnosis is 5 mo (range, 0–25 mo). In 75% of cases, the first EIM manifested after IBD diagnosis (median, 92 mo; range, 29–183 mo). Thirty years after diagnosis up to 50% of patients with IBD have suffered from at least 1 EIM.<sup>15</sup>



**TABLE 3.** Treatment Options of EIM in IBD

EIM Organ	Specific EIM	First-line Therapy	Second-line Therapy	References
Joints	Peripheral arthritis	Intraarticular/oral steroids, sulfasalazine, immunomodulators, COX-2 inhibitors; treatment of IBD flare (type 1)	IFX, adalimumab	Generini et al <sup>32</sup>
	Type 1 (large joints)			Herfarth et al <sup>33</sup>
	Type 2 (small joints)			Atzeni et al <sup>34</sup>
	Axial arthropathies	Physiotherapy, COX-2 inhibitors, MTX, sulfasalazine	IFX, adalimumab	Sarzi-Puttini et al <sup>35</sup>
	Ankylosing spondylitis			Kaufmann et al <sup>36</sup>
Skin	Sacroileitis			Generini et al <sup>32</sup>
	Pyoderma gangrenosum	Oral steroids, cyclosporine, immunosuppressives	IFX, adalimumab	Brooklyn et al <sup>37</sup>
	Erythema nodosum	Treatment of IBD flare	IFX, adalimumab	Kaufmann et al <sup>36</sup> Regueiro et al <sup>38</sup>
	Sweet's syndrome	Topical/systemic steroids	IFX	In Bechet's disease Tanida et al <sup>39</sup>
	Aphthous ulcers	Treatment of IBD flare, topical steroids, oral steroids, topical lidocaine	IFX	Vanbiervliet et al <sup>40</sup> Kaufman et al <sup>35</sup>
Liver	PSC	Endoscopic retrograde cholangiography for dilatation of dominant strictures, UDCA up to 15 m/kg, controversial for high dose	Transplantation	Singh et al <sup>41</sup>
Eyes	Uveitis	Topical/systemic steroids, cyclosporine	IFX	Fries et al <sup>42</sup> Hernandez Garfella <sup>43</sup>
	Episcleritis	Treatment of IBD flare, topical steroids		In Bechet's disease Lakatos <sup>44</sup>

Adapted from Lakatos et al.<sup>44</sup>

because of the reported association of exacerbation of IBD with NSAID use.<sup>46–50</sup>

In a study by Takeuchi et al, up to 25% of patients in remission experienced a disease flare when provided certain NSAIDs. It seems that COX-2 inhibitors may show a better safety profile and might be used with caution in patients with IBD suffering from peripheral arthropathies.<sup>49,51–54</sup>

Whether a discrimination of type I and type II arthropathy is clinically useful and meaningful has never been studied in detail. In most large IBD centers, this discrimination is not used. In fact, affection of small joints may disappear as well with the treatment of the underlying disease, whereas inflammation of the large joints may also occur as side effect of anti-TNF therapy. A careful documentation of joint affections, which is standard in rheumatology, certainly would be helpful and could improve the outcome of patients with IBD. This should be requested as a standard in IBD centers.

### Axial Arthropathies

Axial arthropathies are less frequent than peripheral arthralgia/arthritis in patients with IBD, occurring in 3% to 5%

of patients although frequencies of up to 25% have been reported.<sup>9–13,55</sup> Males are more frequently affected than females. In contrast to peripheral arthralgia/arthritis (at least in contrast to type I arthropathy), axial arthropathies are usually independent of the intestinal IBD activity. Axial arthropathies can be categorized into ankylosing spondylitis and sacroiliitis. Ankylosing spondylitis in patients with IBD occurs in 5% to 10% of patients and is mainly HLA-B27–positive.<sup>10,56,57</sup> Patients with ankylosing spondylitis often experience severe onset of back pain at young age, usually associated with morning stiffness or pain exacerbation by periods of rest. Physical examination reveals limited spinal flexion (Schober's test) and reduced chest expansion. Radiographs in early stages may be normal or show only minimal sclerosis. The disease course is usually progressive, resulting in permanent skeletal damage. Patients with IBD with advanced ankylosing spondylitis may show squaring of vertebral bodies, marginal syndesmophytes, bone proliferation, and ankylosis, features classically described as bamboo spine.

Sacroiliitis is observed radiographically in up to 25% of patients.<sup>6,48</sup> Most patients with sacroiliitis are HLA-B27–negative

and do not progress to ankylosing spondylitis. Patients with the radiographic finding of bilateral sacroiliitis are more likely to progress to ankylosing spondylitis.<sup>58</sup>

Treatment options of peripheral arthralgia/arthritis and axial arthropathies in IBD are summarized in Table 3. Therapeutic agents for axial arthropathies that have been reported include sulfasalazine, mesalamine, methotrexate (MTX), azathioprine, thalidomide, and anti-tumor necrosis factor therapy.<sup>32,59–61</sup> TNF-antibodies such as infliximab and adalimumab have shown an improvement of axial arthropathies in several studies in patients with IBD and should be used especially in refractory cases.<sup>31,32,44,61–64</sup>

Axial arthropathies can impact work ability and cause an additional burden for patients with IBD. The diagnosis of axial arthropathies is followed by an access to medications that frequently are not approved for the treatment of patients with IBD. The treatment of axial arthropathies frequently is initiated by rheumatologists. However, it needs to be highlighted that this has to happen in close collaboration with the gastroenterologist. Enbrel, which has been found not to be effective in IBD, is not a good treatment option for ankylosing spondylitis in patients with IBD.

## EIM OF THE SKIN

The diagnosis of cutaneous EIM in IBD is based on the clinical picture and on their characteristic features and the exclusion of other specific skin disorders. Cutaneous disorders associated with IBD occur in up to 15% of patients.<sup>11,14</sup>

### Erythema Nodosum

Erythema nodosum occurs in up to 15% of patients with CD and 10% of patients with UC.<sup>11</sup> Other publications report a considerably lower frequency.<sup>4,14,65</sup> Preponderance in female patients has been suggested.<sup>65,66</sup> Furthermore, erythema nodosum is frequently associated with eye and joint involvement, isolated colonic involvement, and pyoderma gangrenosum.<sup>65</sup>

Erythema nodosum is usually easily recognized as raised, tender, red, or violet inflammatory subcutaneous nodules of 1 to 5 cm in diameter, typically on the anterior extensor surface of the lower extremities but rarely on the face and trunk.<sup>11</sup> It shows preponderance in females and patients with CD.<sup>14,66</sup> Unpublished data from the Swiss IBD Cohort Study indicate that location of erythema nodosum does not differ significantly between patients with CD and UC. Figure 3 illustrates the distribution of erythema nodosum lesions in male and female patients with IBD. The diagnosis is established based on clinical judgment, and skin biopsies are rarely required. Erythema nodosum usually heals without scars. Its onset coincides with acute flares of IBD and is frequently self-limiting or improves with treatment of the underlying IBD.<sup>13</sup> Mild cases may be treated with leg elevation, use of analgesics, potassium iodine, systemic corticosteroids, and compression stockings.<sup>67</sup>

In severe or refractory cases, alternative causes of erythema nodosum should be investigated such as infections with

*Streptococcus*, *Yersinia pseudotuberculosis*, *Yersinia enterocolitica*, syphilis, sarcoidosis, Behcet's disease, and use of oral contraceptives or other medication. After exclusion of other causes, severe cases may require systemic corticosteroids or immunosuppressive therapy or TNF antibodies. Only a few case reports highlight the benefit of infliximab and adalimumab for erythema nodosum.<sup>68–71</sup> Please refer to Table 3 for an overview of treatment options of EIM in IBD.

### Pyoderma Gangrenosum

Pyoderma gangrenosum is a much rarer, more severe, debilitating EIM, more common in UC than in CD. It affects women more frequently than men<sup>72,73</sup> and is associated with black African origin, familial history of UC, and pancolitis as the initial location of IBD, permanent stoma, eye involvement, and erythema nodosum.<sup>65</sup> The prevalence of pyoderma gangrenosum in IBD is 0.4% to 2%.<sup>4,6,14,66,74</sup> Vice versa, up to 50% of patients with pyoderma gangrenosum have underlying IBD.<sup>1</sup> The lesions are usually preceded by a trauma (even many years earlier) through a phenomenon known as pathergy. This trauma can even be minimal such as venous puncture or biopsy. Figure 4 shows the distribution of location of pyoderma gangrenosum lesions in male and female patients suffering from IBD in the SIBDCS.

Patients with severe disease and colonic involvement are most likely to develop this complication.<sup>75</sup> The disease course is unpredictable. Pyoderma gangrenosum usually begins as an erythematous pustule or nodule that spreads rapidly to the adjacent skin and develops into a burrowing ulcer with irregular violaceous edges.<sup>76</sup> The deep ulcerations often contain purulent material, which is sterile on culture. These ulcers can be solitary or multiple, unilateral, or bilateral, and can range in size from several centimeters to an entire limb. The most common sites include extensor surfaces of the legs (shins) and adjacent to a postsurgical stoma but can occur anywhere on the body, including the genitalia.<sup>75</sup> Peristomal pyoderma gangrenosum is seen occasionally as a complication in patients with IBD. One study followed 20 consecutive peristomal pyoderma gangrenosum patients and reported only limited success with local enterostomal care, debridement, and/or stomal revision but responded to a variety of medical therapies.<sup>77</sup> All these peristomal ulcers healed completely within a median of 11.4 months (range, 1–42 mo). Another smaller study reported on 7 patients with peristomal pyoderma gangrenosum,<sup>78</sup> 4 of which occurred in patients with IBD. Intravenous cyclosporine and infliximab were tried in some of those patients with success.

Cases of pyoderma gangrenosum evolving from preceding erythema nodosum also have been reported.<sup>79</sup> The diagnosis is made clinically, although wound swabs and a skin biopsy may be needed to exclude other conditions. There are no pathognomonic histological features, generally revealing only diffuse neutrophil infiltration and dermolysis. Pyoderma gangrenosum has typically no association to the clinical activity of the underlying intestinal disease; however, pyoderma gangrenosum may resolve with treatment of the IBD. Up to 36% to 50% of patients with pyoderma

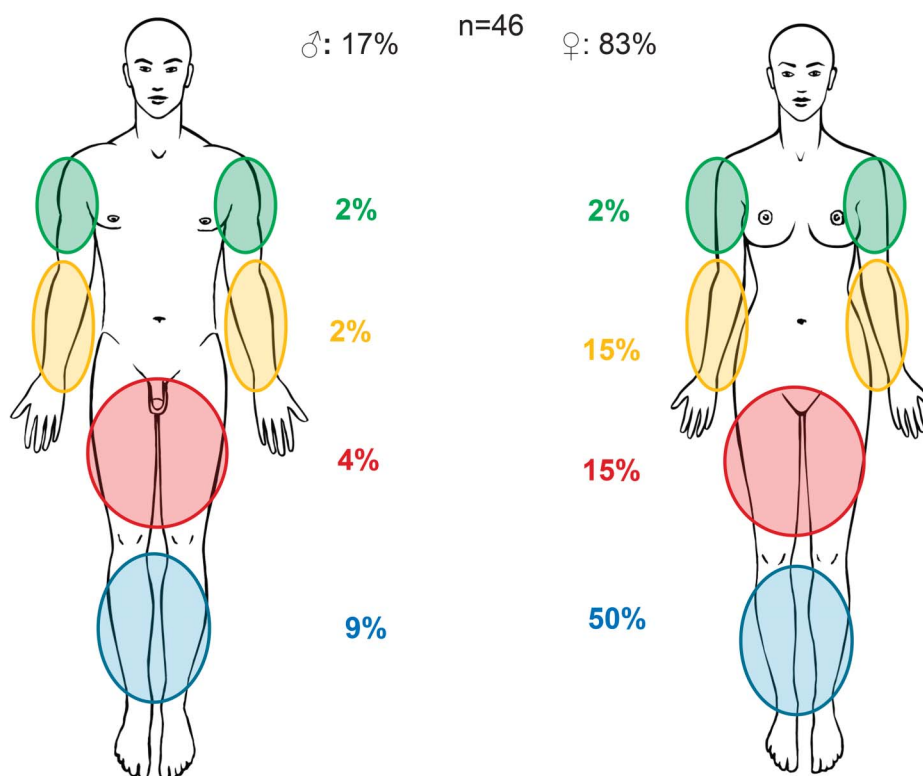


FIGURE 3. Unpublished data from the Swiss IBD cohort study.<sup>15</sup> Location of erythema nodosum in male and female patients suffering from IBD.

gangrenosum have IBD.<sup>80</sup> Pyoderma gangrenosum may resolve with treatment of the underlying IBD (Table 3). Mild cases usually respond to local and topical therapy, including intralesional corticosteroid injections, moist treatment with hydroactive dressings, and topical sodium cromoglycate.<sup>76,81,82</sup> Effective systemic agents include oral sulfasalazine, dapsone, corticosteroids, and immunomodulators such as azathioprine, cyclophosphamide, cyclosporine, methotrexate, tacrolimus, and mycophenolate mofetil.<sup>67,76,81,83,84</sup>

Rapid healing of these lesions should be the therapeutic aim because pyoderma gangrenosum can be a debilitating skin disorder. However, response to therapy varies, and many patients with pyoderma gangrenosum have a disease course that is refractory to these agents. Adalimumab and infliximab are efficient treatment options in severe pyoderma gangrenosum cases and have been reported in several case reports and case series.<sup>35–37,64,77,78,85–105</sup> For an overview on TNF-antibody therapies in EIM, please see Vavricka et al.<sup>64</sup>

PG is initially sometimes treated by surgical debridement. A surgical intervention typically worsens PG. If there is any doubt about the nature of an ulcer in patients with IBD, surgical debridement should be avoided until a PG is excluded. It has been discussed whether a maintenance treatment also is necessary for PG.

### Sweet's Syndrome

Sweet's syndrome, or acute febrile neutrophilic dermatosis, is a rare dermatologic manifestation associated with CD and

UC.<sup>106,107</sup> Besides IBD, Sweet's syndrome may also be associated with other systemic diseases such as malignancy. The cutaneous lesion of Sweet's syndrome manifests as tender or papulosquamous exanthema or nodules involving the arm, legs, trunk, hands, or face. Other characteristic features of Sweet's syndrome are leukocytosis and histologic findings of a neutrophilic infiltrate. Associated systemic manifestations include arthritis, fever, and ocular symptoms, such as conjunctivitis. Its association with IBD usually parallels the gastrointestinal disease activity but may precede the diagnosis of IBD.<sup>108</sup> The use of azathioprine has been implicated in the development of Sweet's syndrome in a patient with IBD.<sup>109,110</sup> Table 3 reports on the treatment options of EIMs in IBD. Most cases of Sweet's syndrome respond to topical or systemic corticosteroid therapy<sup>111</sup> and heal without scarring. Metronidazole has been reported to be effective in 1 case report.<sup>108</sup>

### Oral Lesions

The oral cavity is frequently affected in patients with IBD, especially the ones suffering from CD. Periodontitis and other lesions such as aphthous stomatitis and, in more severe cases, pyostomatitis vegetans are found in up to 10% of patients with IBD.<sup>10,14,112</sup> Both diseases follow the course of the underlying IBD. Aphthous lesions are typically located on the labial and buccal mucosa but may also affect the tongue and oropharynx. Pyostomatitis vegetans manifests as multiple pustular sometimes hemorrhagic eruptions anywhere on the oral mucosa with

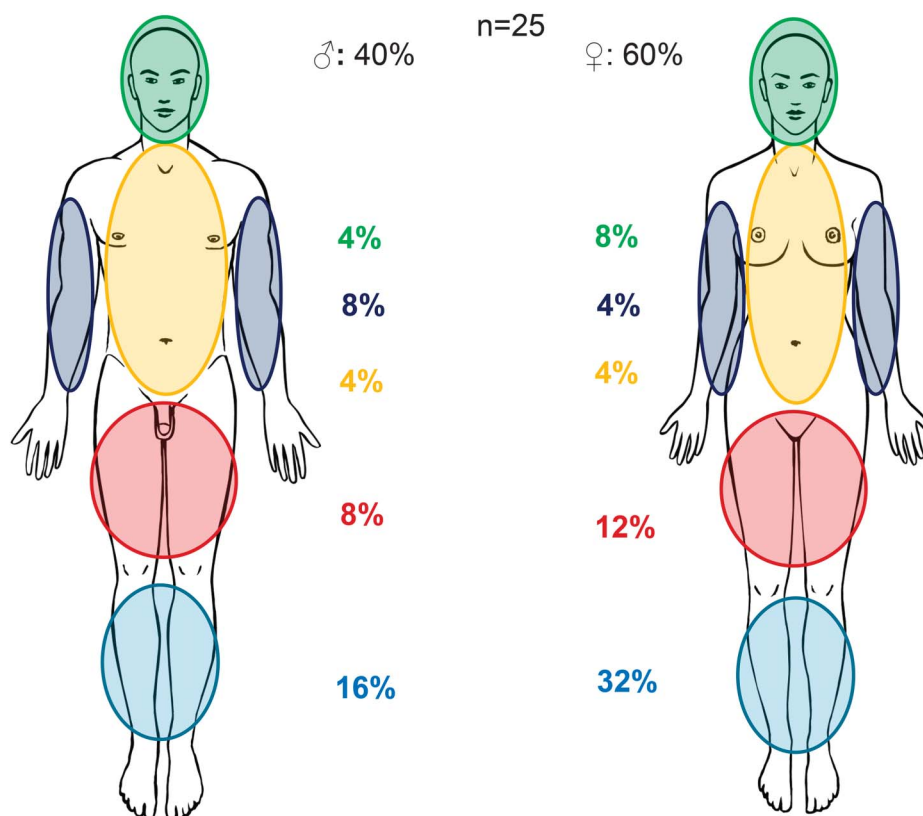


FIGURE 4. Unpublished data from the Swiss IBD cohort study.<sup>15</sup> Location of pyoderma gangrenosum in male and female patients suffering from IBD.

a cobblestone pattern. Therapy includes antiseptic mouthwashes and topical steroids (Table 3).<sup>67,105</sup>

## OCULAR MANIFESTATIONS

Beside joints and skin, the eye is the third major tissue type predisposed to immune-mediated EIMs. Nearly, 2% to 5% of patients with IBD experience ocular manifestations,<sup>10,13,113</sup> particularly associated with concomitant musculoskeletal manifestations.<sup>4</sup> Ocular manifestations are reported more frequently in patients with CD (3.5%–6.3%) than patients with UC (1.6%–4.6%) and include episcleritis and uveitis.<sup>9,11,13,14,55</sup> Patients older than 40 years have more likely iritis/uveitis than those younger than 40 years.<sup>6</sup>

Episcleritis is defined as painless hyperemia of the conjunctiva and sclera without changes of virus and often parallels the activity of the underlying IBD. Besides episcleritis, anterior uveitis is the most common ocular manifestations of IBD. The different types of uveitis are divided as follows: (1) anterior uveitis has its primary site of inflammation in the anterior chamber, (2) intermediate uveitis with its primary site of inflammation being the vitreous, (3) posterior uveitis with its primary site of inflammation being the retina and the choroid, and (4) panuveitis with its primary site of inflammation including anterior chamber, vitreous, retina, and choroid. Uveitis occurs independently of disease activity and is defined as inflammation of the middle chamber of the eye. Uveitis occurs acutely or subacutely and is usually very painful. Anterior

uveitis is also referred to as iritis, which typically presents as pain, photophobia, and red eye and can be associated with blurry vision or floaters. Diagnosis is confirmed by slit-lamp examination. An increasing number of case reports and pilot studies exist on the therapy of uveitis and episcleritis; however, only few reports focus on patients with IBD.<sup>42,114–124</sup>

## Episcleritis and Scleritis

Episcleritis is more common in CD than in UC.<sup>1</sup> It is characterized by acute hyperemia, irritation, burning, and tenderness. Episcleritis usually does not need specific treatment other than those for the underlying disease. Scleritis affects the deeper layers of the eye and can cause visual impairment if not diagnosed early. Patients often complain of severe pain associated with tenderness to palpation.<sup>125</sup> Recurrent scleritis can lead to scleromalacia, retinal detachment, or optic nerve swelling. If therefore mandates aggressive treatment. Disease-specific treatment and topical steroid therapy usually provide prompt relief of symptoms (Table 3).

In case of impairment of vision, the presence of scleritis must be suspected, and prompt referral to an ophthalmologist is mandatory to avoid vision loss.

## Uveitis

Uveitis is less common than episcleritis and occurs in 0.5% to 3% of patients with IBD.<sup>4</sup> When associated with UC, it is



frequently bilateral, insidious in onset, and long-lasting.<sup>4</sup> It presents as ocular pain, blurred vision, photophobia, and headaches. In contrast to episcleritis, the temporal correlation of uveitis with IBD is less predictable, and its occurrence may precede the diagnosis of IBD. On slit-lamp examination, uveitis presents as a perilimbic edema and inflammatory flare in the anterior chamber.<sup>125</sup> Prompt diagnosis and treatment with topical and systemic corticosteroids is necessary to prevent progression to blindness. Steroid refractory cases are treated with cyclosporine A (Table 3). Successful use of infliximab for IBD-associated uveitis was demonstrated in a patient with CD with uveitis and sacroileitis.<sup>42</sup>

## HEPATOBIILIARY EIM

Up to 50% of patients with IBD are affected by hepatobiliary manifestations during the course of their disease.<sup>5</sup> PSC, small-duct PSC, fatty liver disease, granulomatous hepatitis, autoimmune liver and pancreas disease, cholestasis, gallstone formation, and liver injury are hepatobiliary manifestations of IBD.<sup>126</sup>

## PSC Is the Most Frequent Biliary Manifestation of IBD

It is more common in patients with UC than in CD. Approximately, 2.4% to 7.5% of patients with UC are diagnosed with PSC.<sup>127,128</sup> Conversely, 75% of patients with PSC suffer from IBD, typically UC.<sup>129,130</sup> PSC manifests with inflammation and fibrosis of the biliary system that presents clinically with a chronic cholestatic disease. A cholestatic biochemical profile is seen, and characteristic features are frequently found on cholangiography. These include multifocal bile duct strictures and segmental dilatation. PSC can precede the diagnosis of IBD; however, some patients are even diagnosed with PSC several years after proctocolectomy due to UC.<sup>3</sup>

Patients with PSC should undergo colonoscopy to evaluate concomitant IBD. Extensive involvement of the colon with rectal sparing, backwash ileitis in UC, and predominance in male patients are typical features of PSC.<sup>3,130</sup> Patients with PSC can develop bouts of acute cholangitis and ultimately progress to cirrhosis, portal hypertension, and acute decompensation.<sup>131</sup> Interestingly, the diagnosis of PSC seems to influence the course of IBD, as patients with both PSC and UC are suggested to have a milder course of their colitis with less histological inflammation of the colon than patients without PSC.<sup>132</sup> Nevertheless, the presence of PSC is an independent risk factor for the development of colorectal dysplasia and/or cancer in patients with IBD, leading to the recommendation for annual surveillance colonoscopies in affected patients from the time of first diagnosis of IBD.<sup>133–135</sup> The natural course of PSC is independent of IBD, and the bile duct damage is irreversible and nonresponsive to medication. Ursodeoxycholic acid is used widely in patients with PSC; however, only limited effect has been shown. Ursodeoxycholic acid is reported to improve liver enzymes; however, the disease course of PSC is not changed.<sup>136</sup> Some patients with dominant strictures on endoscopic retrograde cholangiography might improve with

dilatation. The majority of patients with PSC ultimately require liver transplantation.

## CONCLUSIONS

IBD is a systemic disease, and EIM are the proof that IBD is not only limited to the gut. Those EIM may affect multiple organs beyond the intestine. Sometimes, these EIM can even be more debilitating than the intestinal disease. Careful screening for EIMs in these patients and early appropriate diagnosis are imperative to prevent morbidity. In EIM responding to the underlying IBD, sufficient IBD therapy and careful monitoring of the EIM is often enough to improve symptoms of the EIM. In EIM not after the activity of the underlying IBD, a multidisciplinary approach is often needed. Clinicians who care for patients with IBD must recognize those various systemic manifestations, as failure to diagnose and treat them early may result in major morbidity.

## REFERENCES

1. Rothfuss KS, Stange EF, Herrlinger KR. Extraintestinal manifestations and complications in inflammatory bowel diseases. *World J Gastroenterol*. 2006;12:4819–4831.
2. Trikudanathan G, Venkatesh PG, Navaneethan U. Diagnosis and therapeutic management of extra-intestinal manifestations of inflammatory bowel disease. *Drugs*. 2012;72:2333–2349.
3. Navaneethan U, Shen B. Hepatopancreatobiliary manifestations and complications associated with inflammatory bowel disease. *Inflamm Bowel Dis*. 2010;16:1598–1619.
4. 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.
5. Danese S, Semeraro S, Papa A, et al. Extraintestinal manifestations in inflammatory bowel disease. *World J Gastroenterol*. 2005;11:7227–7236.
6. Bernstein CN, Blanchard JF, Rawsthorne P, et al. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. *Am J Gastroenterol*. 2001;96:1116–1122.
7. Ricart E, Panaccione R, Loftus EV Jr, et al. Autoimmune disorders and extraintestinal manifestations in first-degree familial and sporadic inflammatory bowel disease: a case-control study. *Inflamm Bowel Dis*. 2004;10:207–214.
8. Mendoza JL, Lana R, Taxonera C, et al. [Extraintestinal manifestations in inflammatory bowel disease: differences between Crohn's disease and ulcerative colitis [Article in Spanish]. *Med Clin (Barc)*. 2005;125:297–300.
9. Rankin GB, Watts HD, Melnyk CS, et al. National Cooperative Crohn's Disease Study: extraintestinal manifestations and perianal complications. *Gastroenterology*. 1979;77:914–920.
10. Su CG, Judge TA, Lichtenstein GR. Extraintestinal manifestations of inflammatory bowel disease. *Gastroenterol Clin North Am*. 2002;31:307–327.
11. Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. *Medicine*. 1976;55:401–412.
12. Farmer RG, Hawk WA, Turnbull RB Jr. Clinical patterns in Crohn's disease: a statistical study of 615 cases. *Gastroenterology*. 1975;68:627–635.
13. Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. *J Clin Gastroenterol*. 1996;23:29–34.
14. Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol*. 2011;106:110–119.
15. Vavricka SR, Gantenbein C, Spoerri M, et al. Chronological order of appearance of extraintestinal manifestations relative to the time of IBD



- diagnosis in the Swiss Inflammatory Bowel Disease Cohort. *Inflamm Bowel Dis*. 2015;21:1794–1800.
16. Ardizzone S, Puttini PS, Cassinotti A, et al. Extraintestinal manifestations of inflammatory bowel disease. *Dig Liver Dis*. 2008;40 (suppl 2):S253–S259.
  17. Biancone L, Mandal A, Yang H, et al. Production of immunoglobulin G and G1 antibodies to cytoskeletal protein by lamina propria cells in ulcerative colitis. *Gastroenterology*. 1995;109:3–12.
  18. Das KM, Sakamaki S, Vecchi M, et al. The production and characterization of monoclonal antibodies to a human colonic antigen associated with ulcerative colitis: cellular localization of the antigen by using the monoclonal antibody. *J Immunol*. 1987;139:77–84.
  19. Geng X, Biancone L, Dai HH, et al. Tropomyosin isoforms in intestinal mucosa: production of autoantibodies to tropomyosin isoforms in ulcerative colitis. *Gastroenterology*. 1998;114:912–922.
  20. Bhagat S, Das KM. A shared and unique peptide in the human colon, eye, and joint detected by a monoclonal antibody. *Gastroenterology*. 1994;107:103–108.
  21. Das KM, Vecchi M, Sakamaki S. A shared and unique epitope(s) on human colon, skin, and biliary epithelium detected by a monoclonal antibody. *Gastroenterology*. 1990;98:464–469.
  22. Satsangi J, Grootsholten C, Holt H, et al. Clinical patterns of familial inflammatory bowel disease. *Gut*. 1996;38:738–741.
  23. Roussomoustakaki M, Satsangi J, Welsh K, et al. Genetic markers may predict disease behavior in patients with ulcerative colitis. *Gastroenterology*. 1997;112:1845–1853.
  24. Ott C, Scholmerich J. Extraintestinal manifestations and complications in IBD. *Nat Rev Gastroenterol Hepatol*. 2013;10:585–595.
  25. Orchard TR, Thiagaraja 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.
  26. Mallas EG, Mackintosh P, Asquith P, et al. Histocompatibility antigens in inflammatory bowel disease. Their clinical significance and their association with arthropathy with special reference to HLA-B27 (W27). *Gut*. 1976;17:906–910.
  27. Smale S, Natt RS, Orchard TR, et al. Inflammatory bowel disease and spondylarthropathy. *Arthritis Rheum*. 2001;44:2728–2736.
  28. Gravallesse EM, Kantrowitz FG. Arthritic manifestations of inflammatory bowel disease. *Am J Gastroenterol*. 1988;83:703–709.
  29. Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. *Gut*. 1998;42:387–391.
  30. Rodriguez-Reyna TS, Martinez-Reyes C, Yamamoto-Furusho JK. Rheumatic manifestations of inflammatory bowel disease. *World J Gastroenterol*. 2009;15:5517–5524.
  31. Brakenhoff LK, van der Heijde DM, Hommes DW. IBD and arthropathies: a practical approach to its diagnosis and management. *Gut*. 2011;60:1426–1435.
  32. Generini S, Giacomelli R, Fedi R, et al. Infliximab in spondyloarthropathy associated with Crohn's disease: an open study on the efficacy of inducing and maintaining remission of musculoskeletal and gut manifestations. *Ann Rheum Dis*. 2004;63:1664–1669.
  33. Herfarth H, Obermeier F, Andus T, et al. Improvement of arthritis and arthralgia after treatment with infliximab (Remicade) in a German prospective, open-label, multicenter trial in refractory Crohn's disease. *Am J Gastroenterol*. 2002;97:2688–2690.
  34. Atzeni F, Ardizzone S, Bertani L, et al. Combined therapeutic approach: inflammatory bowel diseases and peripheral or axial arthritis. *World J Gastroenterol*. 2009;15:2469–2471.
  35. Sarzi-Puttini P, Antiville M, Marchesoni A, et al. Efficacy and safety of anti-TNF agents in the Lombardy rheumatoid arthritis network (LORHEN). *Reumatismo*. 2008;60:290–295.
  36. Kaufman I, Caspi D, Yeshurun D, et al. The effect of infliximab on extraintestinal manifestations of Crohn's disease. *Rheumatol Int*. 2005;25:406–410.
  37. Brooklyn TN, Dunnill MG, Shetty A, et al. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. *Gut*. 2006;55:505–509.
  38. 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.
  39. Tanida S, Inoue N, Kobayashi K, et al. Adalimumab for the treatment of Japanese patients with intestinal Behcet's disease. *Clin Gastroenterol Hepatol*. 2015;13:940–948.
  40. Vanbiervliet G, Anty R, Schneider S, et al. Sweet's syndrome and erythema nodosum associated with Crohn's disease treated by infliximab [Article in French]. *Gastroenterol Clin Biol*. 2002;26:295–297.
  41. Singh S, Khanna S, Pardi DS, et al. Effect of ursodeoxycholic acid use on the risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2013;19:1631–1638.
  42. Fries W, Giofre MR, Catanoso M, et al. Treatment of acute uveitis associated with Crohn's disease and sacroileitis with infliximab. *Am J Gastroenterol*. 2002;97:499–500.
  43. Calvo-Rio V, Blanco R, Beltran E, et al. Anti-TNF-alpha therapy in patients with refractory uveitis due to Behcet's disease: a 1-year follow-up study of 124 patients. *Rheumatology (Oxford)*. 2014;53:2223–2231.
  44. Lakatos PL, Lakatos L, Kiss LS, et al. Treatment of extraintestinal manifestations in inflammatory bowel disease. *Digestion*. 2012;86(suppl 1):28–35.
  45. Clegg DO, Reda DJ, Abdellatif M. Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondylarthropathies: a Department of Veterans Affairs cooperative study. *Arthritis Rheum*. 1999;42:2325–2329.
  46. Bjarnason I, Hayllar J, MacPherson AJ, et al. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. *Gastroenterology*. 1993;104:1832–1847.
  47. Kaufmann HJ, Taubin HL. Nonsteroidal anti-inflammatory drugs activate quiescent inflammatory bowel disease. *Ann Intern Med*. 1987;107:513–516.
  48. Miner PB Jr. Factors influencing the relapse of patients with inflammatory bowel disease. *Am J Gastroenterol*. 1997;92:1S–4S.
  49. Kefalakes H, Stylianides TJ, Amanakis G, et al. Exacerbation of inflammatory bowel diseases associated with the use of nonsteroidal anti-inflammatory drugs: myth or reality? *Eur J Clin Pharmacol*. 2009;65:963–970.
  50. Takeuchi K, Smale S, Premchand P, et al. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2006;4:196–202.
  51. Sandborn WJ, Stenson WF, Brynskov J, et al. Safety of celecoxib in patients with ulcerative colitis in remission: a randomized, placebo-controlled, pilot study. *Clin Gastroenterol Hepatol*. 2006;4:203–211.
  52. 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.
  53. Mahadevan U, Loftus EV Jr, Tremaine WJ, et al. Safety of selective cyclooxygenase-2 inhibitors in inflammatory bowel disease. *Am J Gastroenterol*. 2002;97:910–914.
  54. El Miedany Y, Youssef S, Ahmed I, et al. The gastrointestinal safety and effect on disease activity of etoricoxib, a selective cox-2 inhibitor in inflammatory bowel diseases. *Am J Gastroenterol*. 2006;101:311–317.
  55. Monsen U, Sorstad J, Hellers G, et al. Extracolonic diagnoses in ulcerative colitis: an epidemiological study. *Am J Gastroenterol*. 1990;85:711–716.
  56. Fornaciari G, Salvarani C, Beltrami M, et al. Musculoskeletal manifestations in inflammatory bowel disease. *Can J Gastroenterol*. 2001;15:399–403.
  57. Brewerton DA, James DC. The histocompatibility antigen (HL-A 27) and disease. *Semin Arthritis Rheum*. 1975;4:191–207.
  58. Braun J, Sieper J. The sacroiliac joint in the spondyloarthropathies. *Curr Opin Rheumatol*. 1996;8:275–287.
  59. Breban M, Gombert B, Amor B, et al. Efficacy of thalidomide in the treatment of refractory ankylosing spondylitis. *Arthritis Rheum*. 1999;42:580–581.
  60. Keyser FD, Mielants H, Veys EM. Current use of biologicals for the treatment of spondyloarthropathies. *Expert Opin Pharmacother*. 2001;2:85–93.

61. Van den Bosch F, Kruithof E, De Vos M, et al. Crohn's disease associated with spondyloarthritis: effect of TNF-alpha blockade with infliximab on articular symptoms. *Lancet*. 2000;356:1821-1822.
62. Ellman MH, Hanauer S, Sitrin M, et al. Crohn's disease arthritis treated with infliximab: an open trial in four patients. *J Clin Rheumatol*. 2001;7:67-71.
63. Zochling J, van der Heijde D, Dougados M, et al. Current evidence for the management of ankylosing spondylitis: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. *Ann Rheum Dis*. 2006;65:423-432.
64. Vavricka SR, Scharl M, Gubler M, et al. Which extraintestinal manifestations of IBD respond to biologics? *Curr Drug Targets*. 2014;15:1064-1073.
65. Farhi D, Cosnes J, Zizi N, et al. Significance of erythema nodosum and pyoderma gangrenosum in inflammatory bowel diseases: a cohort study of 2402 patients. *Medicine*. 2008;87:281-293.
66. Freeman HJ. Erythema nodosum and pyoderma gangrenosum in 50 patients with Crohn's disease. *Can J Gastroenterol*. 2005;19:603-606.
67. Timani S, Mutasim DF. Skin manifestations of inflammatory bowel disease. *Clin Dermatol*. 2008;26:265-273.
68. 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.
69. Ortego-Centeno N, Callejas-Rubio JL, Sanchez-Cano D, et al. Refractory chronic erythema nodosum successfully treated with adalimumab. *J Eur Acad Dermatol Venereol*. 2007;21:408-410.
70. Quin A, Kane S, Ulitsky O. A case of fistulizing Crohn's disease and erythema nodosum managed with adalimumab. *Nat Clin Pract Gastroenterol Hepatol*. 2008;5:278-281.
71. Clayton TH, Walker BP, Stables GI. Treatment of chronic erythema nodosum with infliximab. *Clin Exp Dermatol*. 2006;31:823-824.
72. Jorizzo JL, Solomon AR, Zanolli MD, et al. Neutrophilic vascular reactions. *J Am Acad Dermatol*. 1988;19:983-1005.
73. Bennett ML, Jackson JM, Jorizzo JL, et al. Pyoderma gangrenosum. A comparison of typical and atypical forms with an emphasis on time to remission. Case review of 86 patients from 2 institutions. *Medicine*. 2000;79:37-46.
74. Nguyen GC, Torres EA, Regueiro M, et al. Inflammatory bowel disease characteristics among African Americans, Hispanics, and non-Hispanic Whites: characterization of a large North American cohort. *Am J Gastroenterol*. 2006;101:1012-1023.
75. Orchard T. Extraintestinal complications of inflammatory bowel disease. *Curr Gastroenterol Rep*. 2003;5:512-517.
76. Callen JP. Pyoderma gangrenosum. *Lancet*. 1998;351:581-585.
77. Sheldon DG, Sawchuk LL, Kozarek RA, et al. Twenty cases of peristomal pyoderma gangrenosum: diagnostic implications and management. *Arch Surg*. 2000;135:564-568; discussion 568-569.
78. Hughes AP, Jackson JM, Callen JP. Clinical features and treatment of peristomal pyoderma gangrenosum. *JAMA*. 2000;284:1546-1548.
79. Gellert A, Green ES, Beck ER, et al. Erythema nodosum progressing to pyoderma gangrenosum as a complication of Crohn's disease. *Postgrad Med J*. 1983;59:791-793.
80. Chow RK, Ho VC. Treatment of pyoderma gangrenosum. *J Am Acad Dermatol*. 1996;34:1047-1060.
81. Powell RJ, Holbrook MR, Stevens A. Pyoderma gangrenosum and its treatment. *Lancet*. 1997;350:1720-1721.
82. Trost LB, McDonnell JK. Important cutaneous manifestations of inflammatory bowel disease. *Postgrad Med J*. 2005;81:580-585.
83. Friedman S, Marion JF, Scherl E, et al. Intravenous cyclosporine in refractory pyoderma gangrenosum complicating inflammatory bowel disease. *Inflamm Bowel Dis*. 2001;7:1-7.
84. Wollina U, Haroske G. Pyoderma gangrenosum. *Curr Opin Rheumatol*. 2011;23:50-56.
85. Amott ID, McDonald D, Williams A, et al. Clinical use of Infliximab in Crohn's disease: the Edinburgh experience. *Aliment Pharmacol Ther*. 2001;15:1639-1646.
86. Batres LA, Mamula P, Baldassano RN. Resolution of severe peristomal pyoderma gangrenosum with infliximab in a child with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2002;34:558-560.
87. Ferkolj I, Hocevar A, Golouh R, et al. Infliximab for treatment of resistant pyoderma gangrenosum associated with Crohn's disease. *Acta Dermatovenereol Alp Pannonica Adriat*. 2006;15:173-177.
88. Grange F, Djilali-Bouzzina F, Weiss AM, et al. Corticosteroid-resistant pyoderma gangrenosum associated with Crohn's disease: rapid cure with infliximab. *Dermatology*. 2002;205:278-280.
89. Juillerat P, Christen-Zach S, Troillet FX, et al. Infliximab for the treatment of disseminated pyoderma gangrenosum associated with ulcerative colitis. Case report and literature review. *Dermatology*. 2007;215:245-251.
90. Kiran RP, O'Brien-Ermlich B, Achkar JP, et al. Management of peristomal pyoderma gangrenosum. *Dis Colon Rectum*. 2005;48:1397-1403.
91. Kouklakis G, Moschos J, Leontiadis GI, et al. Infliximab for treatment of pyoderma gangrenosum associated with clinically inactive Crohn's disease. A case report. *Rom J Gastroenterol*. 2005;14:401-403.
92. 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.
93. Fonder MA, Cummins DL, Ehst BD, et al. Adalimumab therapy for recalcitrant pyoderma gangrenosum. *J Burns Wounds*. 2006;5:e8.
94. Martin D, Handler T, McDermott J. Leucocytoclastic vasculitis in severe ulcerative colitis. *Mil Med*. 2011;176:581-583.
95. Lopez San Roman A, Bermejo F, Aldanondo I, et al. Pyoderma gangrenosum associated with ulcerative colitis: response to infliximab. *Rev Esp Enferm Dig*. 2004;96:420-422; 422-424.
96. Sapienza MS, Cohen S, Dimarino AJ. Treatment of pyoderma gangrenosum with infliximab in Crohn's disease. *Dig Dis Sci*. 2004;49:1454-1457.
97. Singh M, Andrew SM, Lear JT. Infliximab as a treatment for recalcitrant pyoderma gangrenosum. *Clin Exp Dermatol*. 2004;29:196-197.
98. Tan MH, Gordon M, Lebwohl O, et al. Improvement of Pyoderma gangrenosum and psoriasis associated with Crohn disease with anti-tumor necrosis factor alpha monoclonal antibody. *Arch Dermatol*. 2001;137:930-933.
99. Triantafyllidis JK, Cheracakis P, Sklavaina M, et al. Favorable response to infliximab treatment in a patient with active Crohn disease and pyoderma gangrenosum. *Scand J Gastroenterol*. 2002;37:863-865.
100. Zaccagna A, Bertone A, Puiatti P, et al. Anti-tumor necrosis factor alpha monoclonal antibody (infliximab) for the treatment of Pyoderma gangrenosum associated with Crohn's disease. *Eur J Dermatol*. 2003;13:258-260.
101. Alkhouri N, Hupertz V, Mahajan L. Adalimumab treatment for peristomal pyoderma gangrenosum associated with Crohn's disease. *Inflamm Bowel Dis*. 2009;15:803-806.
102. Pomerantz RG, Husni ME, Mody E, et al. Adalimumab for treatment of pyoderma gangrenosum. *Br J Dermatol*. 2007;157:1274-1275.
103. Zold E, Nagy A, Devenyi K, et al. Successful use of adalimumab for treating fistulizing Crohn's disease with pyoderma gangrenosum: two birds with one stone. *World J Gastroenterol*. 2009;15:2293-2295.
104. Mimouni D, Anhalt GJ, Kouba DJ, et al. Infliximab for peristomal pyoderma gangrenosum. *Br J Dermatol*. 2003;148:813-816.
105. Thrash B, Patel M, Shah KR, et al. Cutaneous manifestations of gastrointestinal disease: part II. *J Am Acad Dermatol*. 2013;68:211 e211-233; quiz 244-216.
106. Becuwe C, Delaporte E, Colombel JF, et al. Sweet's syndrome associated with Crohn's disease. *Acta Derm Venereol*. 1989;69:444-445.
107. Benton EC, Rutherford D, Hunter JA. Sweet's syndrome and pyoderma gangrenosum associated with ulcerative colitis. *Acta Derm Venereol*. 1985;65:77-80.
108. Banet DE, McClave SA, Callen JP. Oral metronidazole, an effective treatment for Sweet's syndrome in a patient with associated inflammatory bowel disease. *J Rheumatol*. 1994;21:1766-1768.
109. Treton X, Joly F, Alves A, et al. Azathioprine-induced Sweet's syndrome in Crohn's disease. *Inflamm Bowel Dis*. 2008;14:1757-1758.
110. Ali M, Duerksen DR. Ulcerative colitis and Sweet's syndrome: a case report and review of the literature. *Can J Gastroenterol*. 2008;22:296-298.
111. Kemmett D, Hunter JA. Sweet's syndrome: a clinicopathologic review of twenty-nine cases. *J Am Acad Dermatol*. 1990;23:503-507.
112. Vavricka SR, Manser CN, Hediger S, et al. Periodontitis and gingivitis in inflammatory bowel disease: a case-control study. *Inflamm Bowel Dis*. 2013;19:2768-2777.
113. Petrelli EA, McKinley M, Troncale FJ. Ocular manifestations of inflammatory bowel disease. *Ann Ophthalmol*. 1982;14:356-360.

114. Foeldvari I, Nielsen S, Kummerle-Deschner J, et al. Tumor necrosis factor- $\alpha$  blocker in treatment of juvenile idiopathic arthritis-associated uveitis refractory to second-line agents: results of a multinational survey. *J Rheumatol*. 2007;34:1146–1150.
115. Hale S, Lightman S. Anti-TNF therapies in the management of acute and chronic uveitis. *Cytokine*. 2006;33:231–237.
116. Joseph A, Raj D, Dua HS, et al. Infliximab in the treatment of refractory posterior uveitis. *Ophthalmology*. 2003;110:1449–1453.
117. Lindstedt EW, Baarsma GS, Kuijpers RW, et al. Anti-TNF- $\alpha$  therapy for sight threatening uveitis. *Br J Ophthalmol*. 2005;89:533–536.
118. Rajaraman RT, Kimura Y, Li S, et al. Retrospective case review of pediatric patients with uveitis treated with infliximab. *Ophthalmology*. 2006;113:308–314.
119. Sfrikakis PP, Theodossiadis PG, Katsiari CG, et al. Effect of infliximab on sight-threatening panuveitis in Behcet's disease. *Lancet*. 2001;358:295–296.
120. 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.
121. Saurenmann RK, Levin AV, Rose JB, et al. Tumour necrosis factor  $\alpha$  inhibitors in the treatment of childhood uveitis. *Rheumatology*. 2006;45:982–989.
122. Kahn P, Weiss M, Imundo LF, et al. Favorable response to high-dose infliximab for refractory childhood uveitis. *Ophthalmology*. 2006;113:860–864.e862.
123. Biester S, Deuter C, Michels H, et al. Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol*. 2007;91:319–324.
124. Braun J, Baraliakos X, Listing J, et al. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum*. 2005;52:2447–2451.
125. Mintz R, Feller ER, Bahr RL, et al. Ocular manifestations of inflammatory bowel disease. *Inflamm Bowel Dis*. 2004;10:135–139.
126. Yarur AJ, Czul F, Levy C. Hepatobiliary manifestations of inflammatory bowel disease. *Inflamm Bowel Dis*. 2014;20:1655–1667.
127. Olsson R, Danielsson A, Jamerot G, et al. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. *Gastroenterology*. 1991;100:1319–1323.
128. Fausa O, Schrumpf E, Elgjo K. Relationship of inflammatory bowel disease and primary sclerosing cholangitis. *Semin Liver Dis*. 1991;11:31–39.
129. Wiesner RH, LaRusso NF. Clinicopathologic features of the syndrome of primary sclerosing cholangitis. *Gastroenterology*. 1980;79:200–206.
130. Broome U, Bergquist A. Primary sclerosing cholangitis, inflammatory bowel disease, and colon cancer. *Semin Liver Dis*. 2006;26:31–41.
131. Tischendorf JJ, Hecker H, Kruger M, et al. Characterization, outcome, and prognosis in 273 patients with primary sclerosing cholangitis: a single center study. *Am J Gastroenterol*. 2007;102:107–114.
132. Joo M, Abreu-e-Lima P, Farraye F, et al. Pathologic features of ulcerative colitis in patients with primary sclerosing cholangitis: a case-control study. *Am J Surg Pathol*. 2009;33:854–862.
133. 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.
134. Loftus EV Jr, Harewood GC, Loftus CG, et al. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. *Gut*. 2005;54:91–96.
135. Talwalkar JA, Lindor KD. Primary sclerosing cholangitis. *Inflamm Bowel Dis*. 2005;11:62–72.
136. Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. *N Engl J Med*. 1997;336:691–695.