Arthropathies in inflammatory bowel disease : Characteristics and impact on daily functioning

Erp, S.J.H. van

CHAPTER 3

Classifying back pain and peripheral joint complaints in inflammatory bowel disease patients: a prospective longitudinal follow up study

S.J.H. van Erp*, L.K.P.M. Brakenhoff*, F.A. van Gaalen, R. van den Berg, H.H. Fidder, H.W. Verspaget, T.W.J Huizinga, R.A. Veenendaal, R. Wolterbeek, D. van der Heijde, A.E. van der Meulen-de Jong, D.W. Hommes

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** Shared first authorship*

ABSTRACT

Background: Peripheral joint complaints (pJTC) and chronic back pain (CBP) are the most common extra-intestinal manifestations in patients with inflammatory bowel disease (IBD). This prospective study evaluates variables associated with joint/back pain, including IBD disease activity.

Methods: IBD patients with back pain ≥ 3 months and/or peripheral joint pain/swelling (n=155), and IBD patients without joint complaints (n=100; controls), were followed for a period of one year. Patients were classified as having SpondyloArthritis (SpA) according to several sets of criteria. Statistical analysis included logistic regression models and linear mixed model analysis.

Results: Of the 155 patients with joint/back pain, 13 had chronic back pain, 80 peripheral joint complaints and 62 axial and peripheral joint complaints. Smoking, female gender and IBD disease activity were independently associated with IBD joint/back pain. The ASAS criteria for axial and peripheral SpA were fulfilled in 12.3% of patients, with 9.7% (n=15) receiving a rheumatologic diagnosis of arthritis. During the 12-month follow-up, the majority of the amount of patients reporting joint/back pain remained stable.

Conclusion: In our cohort, the majority of IBD patients reported joint/back pain and SpA was relatively common. To facilitate effective care, gastroenterologists should be aware of the various features of SpA to classify joint complaints and by making use of an efficient referral algorithm to refer CBP patients to the rheumatologist.

INTRODUCTION

Arthropathies are the most common extra-intestinal manifestations (EIMs) of inflammatory bowel disease (IBD), affecting approximately 30% of the patients.[1-2] Symptoms may be debilitating and have a considerable impact on quality of life.[3-4] IBD-associated arthropathies can be divided into inflammatory and non-inflammatory joint pain and may involve both axial and peripheral joints. Non-inflammatory joint pain, or arthralgia, is one of the most common complaints in daily IBD practice, but has not yet been studied systematically.[3] Joint and back pain (hereafter referred to as "joint/back pain") are the most important clinical manifestations of IBD-associated arthropathies.

For the gastroenterologist, joint/back pain can be challenging symptoms to diagnose and many have difficulties in differentiating arthralgia from arthritis. Since gastroenterologists are, in general, unfamiliar with the diagnosis and management of joint/back pain, it seems warranted that IBD joint complaints should be classified according to existing rheumatologic standards, thus allowing appropriate multi-disciplinary management. Moreover, gastroenterologists mostly apply the Oxford criteria[5] to classify peripheral joint complaints based on two different types according to articular involvement. Type 1 (oligoarticular) peripheral arthritis included patients with less than five joints involved, evidence of joint swelling and acute, but self-limiting attacks. Type 2 (polyarticular) peripheral arthritis included patients with five or more symmetrical affected joints, joint swelling and a chronic character. Although the Oxford criteria distinguish these two types of peripheral joint complaints, this classification has limited utility for the physician in daily clinical practice. More importantly, these criteria are only applicable to arthritis and not arthralgia. Rheumatologists therefore generally ignore the Oxford criteria and classify arthritis associated with IBD within the group of SpondyloArthritis (SpA) disorders.[6] SpA is a group of rheumatic diseases characterized by inflammation of the spine and the sacroiliac (SI) joints. This often results in pain and/or stiffness of the spine and neck. Besides, inflammation may affect other regions including the peripheral joints, tendons, eyes, skin and/or gut.

In order to develop a multi-disciplinary care pathway for IBD patients with joint complaints, we rigorously characterized peripheral joint complaints (pJTC) and chronic back pain (CBP) according to SpA criteria sets. In addition, we sought to determine which variables were associated with the onset of IBD joint com-

plaints and which predicted long-term outcome. With this aim in mind, we carried out a prospective, longitudinal follow-up study of IBD patients with back pain and/or peripheral joint complaints.

METHODS

Study population

From July 2009 to February 2010, all IBD patients visiting the IBD outpatient clinic of the department of Gastroenterology and Hepatology of the Leiden University Medical Center (LUMC), the Netherlands, were asked to complete a questionnaire to assess the presence of joint complaints. The questions concerned experience of: (1) CBP, defined as back pain for ≥ 3 months, (2) CBP for ≥ 3 months during the last year, (3) current pJTC (pain and/or joint swelling) and (4) pJTC during the last year. Patients with self-reported joint/back pain were then invited to attend the JOINT outpatient clinic, a multidisciplinary clinic dedicated to IBD patients with joint complaints. This clinic was jointly established by the department of Gastroenterology and Hepatology and the department of Rheumatology with the aim of expanding knowledge of IBD joint complaints, especially in the area of diagnosis and medical management. Patients with evident joint swelling and/or radiologic proven sacroiliitis were directly referred for rheumatologic care. All IBD patients without joint/back pain during the previous year served as controls and were also invited to attend the multidisciplinary clinic. To avoid that high inclusion rates would influence the quality of patient care and since only one clinical researcher was able to perform physical and rheumatologic examination, inclusion was limited to 255 patients. The study was approved by the institutional medical ethical committee of the LUMC and patients signed a written informed consent prior to study enrolment.

Study design and data collection

All IBD patients with and without self-reported joint/back pain, who signed informed consent, were seen at the JOINT outpatient clinic at study inclusion and at 1 year follow-up. During the 12-month study period, patients were asked to complete monthly questionnaires assessing IBD disease activity and spine and/or peripheral joint scores. When no response was received within one week a reminder email or letter was sent out, followed by a telephone call.

During the baseline visit, a routine medical history was taken and data of all participants on extra-intestinal manifestations were collected, including common IBD-related eye and skin manifestations, such as acute anterior uveitis and erythema nodosum. The musculoskeletal history included back pain, enthesitis, arthritis and dactylitis. The family history included IBD, SpA (including ankylosing spondylitis (AS)), acute anterior uveitis, psoriasis and reactive arthritis. In addition to the routine physical examination, a rheumatologic examination was performed in all IBD patients by a well-trained clinical researcher, including a detailed assessment of the number of tender and swollen joints. Furthermore, the presence of dactylitis was registered and enthesitis was assessed using the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) index.[7] Assessment of spinal mobility was performed using the modified Schober test, lateral spinal flexion, cervical rotation, occiput-to-wall distance (OWD), chest expansion and the intermalleolar distance.[8] The Bath Ankylosing Spondylitis Metrology Index (BASMI) was calculated, ranging from 0-10.[9] In the BASMI, the tragus-to-wall distance is used and derived from the OWD by adding 8 cm. The value zero in the OWD is equivalent to a score of zero in the BASMI calculation. The higher the BASMI score, the more severe the patient's limitation of axial movement. Spinal disease activity and function was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[10] and the Bath Ankylosing Spondylitis Functional Index (BASFI).[11] Laboratory assessments included ESR and CRP. HLA-B27 was only typed in patients with CBP and/or peripheral joint complaints. Radiographs of the pelvis (anterior-posterior view), the lumbar and cervical spine (lateral view) and radiographs of the most painful peripheral joints were performed in patients with joint/back pain.

Following the baseline assessment, patients were categorized into two study groups:

1. Patients with joint/back pain: CBP for ≥ 3 months and/or pJTC currently or during the previous year.
2. Patients without joint/back pain: no back pain and/or pJTC during the previous year.

Definitions

a. Crohn's Disease (CD) disease activity was assessed according to the Harvey Bradshaw Index (HBI)[12]; Ulcerative Colitis (UC) disease activity was assessed using the Simple Clinical Colitis Activity Index (SCCAI).[13] A score > 4 reflects active disease.

b. Arthralgia was defined as joint pain without swelling; arthritis as joint pain with swelling.
c. Overall and nocturnal pain of the spine and peripheral joint pain during the previous week was separately scored on an 11-point numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain).[14]
d. Disease activity of the spine and disease activity of the peripheral joints during the previous week was scored, separately, on an 11-point NRS where 0 is inactive disease and 10 is extremely active disease.
e. Patients were classified as SpA according to the Amor[15], European Spondyloarthropathy Study Group (ESSG)[16], Assessment of SpondyloArthritis international Society (ASAS)[17-18] and modified New York (mNY) criteria.[19]

SpA classifications

In short, the *Amor criteria* for SpA consist of a scoring system of 8 clinical features (1-2 points per feature), radiographic sacroiliitis (3 points), HLA-B27 (2 points) and a good response to non-steroidal anti-inflammatory drugs (NSAIDs) (2 points). IBD is one of the clinical features receiving 2 points. A score of 6 or more classifies a patient as having SpA. In the *ESSG* criteria, patients with IBD and inflammatory back pain (according to the ESSG standard) and/or arthritis (past or present asymmetric arthritis or arthritis predominantly in the lower limbs) are classified as SpA. *ASAS* developed two SpA criteria sets to classify patients with predominantly axial SpA (axSpA) and with predominantly peripheral SpA (pSpA). Patients with IBD and CBP for ≥ 3 months and age at onset of back pain < 45 years can be classified as axSpA if sacroiliitis on radiograph or MRI is present and/or if HLA-B27 with at least one other SpA feature is present. An IBD patient with arthritis (usually predominantly lower limbs and/or asymmetric arthritis), enthesitis or dactylitis should be classified as pSpA. According to the *mNY criteria*, patients with AS based on radiographic sacroiliitis and the clinical criteria CBP for ≥ 3 months are classified as SpA (see Supplementary data for further details).

Statistics

Continuous variables were described with mean ± standard deviation (SD) and categorical variables as proportions with percentages. T-tests were used for comparing continuous variables among the two study groups and Fisher exact and Chi-square tests were used for comparing categorical variables. Logistic regression models, with joint/back pain as the dependent variable, were used to assess variables associated with joint/back pain in IBD. First, univariate anal-

yses were performed for several variables, including age, gender, type of IBD, IBD-associated surgery, active IBD (HBI or SCCAI > 4), smoking, family history for SpA, and cutaneous, ocular and joint manifestations. Second, variables with a statistical level of $p < 0.1$ in the univariate analyses were included in the multivariate analyses. Linear mixed model analyses were performed to investigate whether IBD disease activity is associated with a worsening (e.g. an increased score) in the following items throughout follow-up: 1) disease activity of the spine; 2) general and nocturnal pain of the spine; 3) disease activity of the peripheral joints; 4) general and nocturnal pain of the peripheral joints. Patients were included as random variables, time points and IBD disease activity as fixed variables, and the outcome measures as dependent variables. All analyses were performed using SPSS version 20. P-values ≤0.05 were considered significant.

RESULTS

Patients

In total, 510 IBD patients completed the questionnaire on joint complaints at the IBD outpatient clinic of the LUMC: 321 patients with Crohn's disease (CD), 186 with ulcerative colitis (UC), and 3 with indeterminate colitis (IC). Of these, 310 (60.8%) patients reported joint complaints: 12% back pain only, 54% pJTC only and 34% both (Figure 1). The percentage of patients complaining about joint pain was highest in CD (65%) compared to UC (49%). Subsequently, since only one clinical researcher was well-trained in the assessment and examination of joint complaints, inclusion was limited to 255 patients (50%). These 255 IBD patients signed informed consent and attended the multidisciplinary clinic, of whom 155 (60.1%) were assigned to the study group with joint/back pain, while 100 (38.8%) patients without joint/back pain served as controls. The clinical and demographic characteristics of all patients are presented in Table 1. For 80-84% of patients, the onset of CBP and pJTC followed the IBD diagnosis and was on average more than a decade after diagnosis, with a trend towards pJTC starting a few years earlier than CBP (Table 1). Only 16-20% developed joint/back pain prior to the diagnosis of IBD. Patients with IBD and joint/back pain were more often diagnosed with CD (p=0.03), were more frequently female (p=0.001), were more often smokers (p=0.001), were more likely to have cutaneous manifestations (psoriasis, erythema nodosum, pyoderma gangrenosum) (p=0.04) and acute anterior uveitis (p=0.02) compared to patients with IBD without joint/back pain. The Montreal classification did not reveal subtypes

more prone for developing joint/back pain. In addition, previous IBD-related surgery or a family history of SpA was not associated with the development of joint/back pain.

Of the 155 patients with joint/back pain, 80 patients (51.6%) reported pJTC only, 13 patients (8.4%) reported CBP only and 62 patients (40.0%) reported axial as well as peripheral joint involvement (Table 2). Over 50% of pJTC patients reported the hand (32.5%) and the knee (17.5%) as the most frequently affected joints, while 80.0% of patients reported involvement of more than one joint. At physical examination, 98 (63.2%) patients had ≥ 1 tender joint(s), while 48 (31.0%) patients had ≥ 1 tender pressure point for enthesitis. Only 52 IBD patients with evident joint swelling and signs of inflammation seen during rheumatologic examination or on the radiographs were referred to the rheumatologist. Based on physical examination performed by the rheumatologist, fifteen patients (9.7%) were diagnosed with arthritis and all could be classified as showing type 1 peripheral joint complaints according to the Oxford criteria. In addition, 1 (0.7%) patient was diagnosed with dactylitis, 1 (0.7%) patient with enthesitis and 2 (1.4%) patients with tendinitis. Following radiographic assessment of all 75 CBP patients, 5 patients (6.7%) showed sacroiliitis and 1 patient was diagnosed with diffuse idiopathic skeletal hyperostosis (DISH) of the lumbar spine. In total, 136/155 (87.7%) patients with self-reported joint/back pain were diagnosed with arthralgia. The mean BASDAI and mean BASFI of CBP patients were 3.1 (SD 1.9) and 2.2 (SD 1.9), respectively. The mean BASMI in pJTC patients with CBP was higher compared to pJTC patients without CBP: 1.7 (SD 0.9) vs. 1.4 (SD 0.8), p=0.03.

Univariate analysis showed that CD (p=0.002), female (p=0.001), smoking (p=0.002), IBD disease activity (p<0.001), cutaneous manifestations (p=0.02) and acute anterior uveitis (p=0.003) were associated with an increased odds ratio (OR) for joint/back pain (Table 3). In the multivariate analysis, the variables female (OR 1.97 (95%CI 1.10-3.53), p=0.02), smoking (2.28 (95%CI 1.10-4.75), p=0.03) and IBD disease activity (OR 4.07 (95%CI 2.23-7.45), p<0.001) remained independently associated with IBD joint/back pain.

Classification

Overall, IBD patients with CBP had on average 1.7 SpA features, pJTC patients 1.4, while IBD patients with both CBP and pJTC had on average 2.3 different SpA features. Based on the various SpA features (Table 2), 155 patients with joint/back pain were classified according to the SpA criteria sets. In total, 28 out of

the 155 patients (18.1%) conformed with more than one classification criteria set, while 63 (40.6%) patients fulfilled any of the SpA criteria sets: 32 (20.6%) patients fulfilled the Amor criteria, 52 (33.5%) patients fulfilled the ESSG criteria, including 37 (71.2%) in the inflammatory back pain arm, 10 the peripheral arm, and 5 both arms. Nineteen (12.3%) patients fulfilled the recently developed ASAS criteria, 6 met the axSpA criteria and 15 met the pSpA criteria (Figure 2). Four (2.6%) patients fulfilled the mNY criteria for AS. These 4 patients also fulfilled the Amor, the ESSG and the ASAS criteria for axial SpA. There were no differences in gender and type of IBD between patients fulfilling any of the SpA criteria sets compared to those who did not fulfil any of the SpA criteria sets (data not shown).

Follow-up

In total, 242/255 (94.9%) patients were seen at the 12-month visit of the joint outpatient clinic (Figure 3); 98 patients without and 144 patients with joint/back pain. Five of 98 patients without joint complaints at baseline developed joint complaints without symptoms or signs of disease activity, while 12 of 144 patients with joint complaints at baseline reported a cessation of joint/back pain at 12 months. Five of the 136 (3.7%) patients with arthralgia at visit 1 developed arthritis, 1/136 (0.7%) developed enthesitis and 1/136 (0.7%) developed tendinitis during the 12-month follow-up period.

A total of 245/255 (96.1%) patients completed all 12 questionnaires to assess IBD disease activity and spine and/or peripheral joint scores: 148/155 patients with and 97/100 patients without joint/back pain. A total of 122/148 (82.4%) IBD patients with joint/back pain completed ≥ 7 questionnaires in which they reported the course of their IBD disease activity and joint complaints in the 12-month follow-up. Of these 122 patients with joint/back pain in the follow-up period, IBD disease activity was continuously in clinical remission in 31.1% of patients, compared to 36.9% with continuous IBD disease activity and 32.0% with intermittent IBD disease activity. Smokers with CD appeared to be prone to developing continuous IBD disease activity, although the difference was not significant ($p=0.08$). In patients with joint/back pain, the HBI scores for general well-being ($p=0.002$), abdominal pain ($p=0.025$), diarrhoea ($p<0.001$), aphthous ulcers ($p=0.03$) and the SCCAI score on nocturnal pain ($p<0.001$) all affected IBD disease activity compared to IBD patients in continuous clinical remission. Patients with continuous IBD disease activity were more likely to be referred to the rheumatologist ($p=0.04$) for their joint complaints.

The linear mixed model analyses demonstrated that IBD disease activity was significantly associated with higher scores for disease activity of the spine, pain and nocturnal pain of the spine, disease activity of the peripheral joints, and pain and nocturnal pain of the peripheral joints over time, with a range of regression coefficients estimated between 0.47-1.52 (all $p \leq 0.05$). Thereafter, we also included type of IBD and gender as fixed factors. CD was only significantly associated with higher scores for pain and nocturnal pain of the peripheral joints (regression coefficients ranged from 0.96-1.00, $p \leq 0.05$). Gender had no significant effect.

DISCUSSION

Since gastroenterologists are not used to the diagnosis and management of joint/back pain, a multidisciplinary approach in co-operation with rheumatologists is necessary.

In this prospective study, 255 IBD patients attended the multidisciplinary IBD JOINT outpatient clinic, including 155 with and 100 without joint/back pain. The patients in the former category reported joint pain, back pain or both and we characterized these complaints in depth. In our cohort, IBD patients reporting joint/back pain were more likely to be diagnosed with CD, were more commonly female, smokers and showed more often cutaneous manifestations and acute anterior uveitis compared to patients without arthropathies. Female gender, smoking and IBD disease activity were independently associated with joint/back pain in IBD. Moreover, IBD disease activity was significantly associated with pain and disease activity of the spine and peripheral joints over time. Although joint/back pain is frequently encountered in IBD patients[1-3,14,20-21], only 12.3% fulfilled the ASAS criteria for SpA, which are most often used in clinical trials.[22] During the 12-month follow-up, the majority of patients showed no change in the presence or absence of joint/back pain. Based on an HBI or SCCAI score above 4, approximately 37% of the joint/back pain patients reported continuous IBD disease activity. A possible explanation for the high proportion described in previous studies[23-25] is that the bulk of the HBI score is due to diary card items (pain, diarrhoea and general well-being). Because the remaining index items (arthralgia, for example) make a proportionately smaller contribution, this may eventually lead to artificially elevated HBI scores. Van der Have et al. showed in this cohort that joint/back pain in IBD patients has a significant negative

impact on quality of life (QoL) and work productivity. This difference remained significant during the follow-up of 12 months.[26]

Gastroenterologists should differentiate SpA patients from non-SpA patients to make a distinction between the patients that should be referred to a rheumatologist and the patients that should remain under supervision of the gastroenterologist. This differentiation may be aided through the use of classification criteria based on the SpA features. Although classification criteria are not intended for use to diagnose SpA in clinical practice, the value of applying classification criteria is to distinguish typical cases of a particular disease using a standardized diagnostic process. Items in classification criteria reflect the essential features of a disease.[27]

Different SpA criteria were evaluated in this study and the finding that more patients complied the ESSG criteria compared to the ASAS and Amor criteria can be attributed to the high number of IBD patients fulfilling the inflammatory back pain criteria according to the ESSG criteria set of criteria. Recent studies by van den Berg et al.[27-28] reported that the ASAS criteria for SpA outperformed the ESSG and Amor criteria. However, this is in contrast with the results described by Cheung et al.[29], where the ASAS criteria failed to perform better in comparison with the Amor and ESSG criteria. A possible explanation for these opposing results is the difference in disease duration in the described cohorts. The longer the disease duration, the more likely it is that symptoms develop.[30]

In our opinion, the ASAS criteria represent the most practical system with which to classify axial and peripheral SpA and are thus particularly applicable in the clinic, because based on this approach, all the subtypes of SpA will be recognized as a distinct disease. In total, 12.3% of patients fulfilled the ASAS criteria for axial and peripheral SpA and should be referred to a rheumatologist. However, the number of patients classified as having axial SpA by the ASAS criteria is probably an underestimate in this study, because the axial SpA has not been proven by MRI.

Gastroenterologists need an efficient referral algorithm that can be applied to IBD patients with CBP. In total, 75 patients had CBP, although not all of them were suspicious for axial SpA. Based on the Berlin algorithm[31], we propose a modified referral algorithm for IBD patients with suspected axial SpA that can be utilized by gastroenterologists in the clinic to distinguish patients with a high

probability of axial SpA from low risk patients (Figure 4). This proposed algorithm should be validated in future studies in an IBD cohort with joint/back pain.

Orchard et al. proposed the Oxford criteria for IBD patients with peripheral joint complaints. These criteria are often used by gastroenterologists since they are unfamiliar with the diagnosis and management of joint/back pain in patients with IBD.[5] However, rather than using the Oxford criteria, which mainly focus on peripheral joint complaints, joint/back pain in IBD patients is best categorized into SpA and non-SpA. This is also emphasized in our cohort, with only 15 patients (9.7%) fulfilling the Oxford criteria. Use of the Oxford criteria increases the chance that SpA patients with an axial component will be neglected.
Patients who do not fulfil the arthritis criteria can be classified as having arthralgia. Like most of the IBD patients with joint/back pain, these patients remain under the supervision of a gastroenterologist. As few gastroenterologists have the necessary expertise to correctly manage joint/back pain, an arthralgia treatment algorithm is also needed. Joint pain influences patient QoL and a better understanding of disease aetiology contributes to a better QoL.[26] Therefore, patients with arthralgia should be informed and educated about their symptoms. For example, smoking is independently associated with joint/back pain and thus patients should be aware that smoking increases the risk of development of joint complaints. Besides providing adequate information, effective interventions should be recommended. Physiotherapy is one intervention that can maintain or stimulate the flexibility of the joints without adverse effects. Studies have demonstrated the effectiveness of physiotherapy in patients with joint/back pain and the subsequent improvement of mobility of the joints.[32-34] Due to the common inflammatory pathways and the role of cytokines in IBD and arthropathies, IBD-related medication may also have a positive effect on joint complaints.[35]

We have shown that joint/back pain is correlated with IBD disease activity. Thus, a 'treat to target' strategy, including mucosal healing, could prove valuable in controlling symptoms of joint/back pain.[36-37] Future studies should evaluate the impact of mucosal healing on IBD-related joint/back pain.

In conclusion, proper classification and management of joint/back pain is a challenging task for gastroenterologists. Classification should be performed using existing rheumatologic standards to further enhance multidisciplinary management in SpA positive patients. Future approaches to IBD-associated

joint/back pain should include care pathways guided by treatment algorithms applicable to the daily practice of the gastroenterologist.

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TABLES AND FIGURES

Table 1. Clinical and demographic characteristics of the study population at baseline.

	IBD with joint/ back pain (n=155)	IBD without joint/ back pain (n=100)	P-value
Type of IBD, n (%)			
Crohn's disease	121 (78.1)	65 (65.0)	0.03
Ulcerative colitis	34 (21.9)	35 (35.0)	
Male, n (%)	46 (29.7)	51 (51.0)	0.001
Age at inclusion (years), mean ± SD	43.4 ± 13.6	42.7 ± 13.5	0.71
Age of IBD onset (years), mean ± SD	27.5 ± 11.3	26.0 ± 10.0	0.28
IBD disease duration (years), mean ± SD	15.4 ± 11.8	16.2 ± 11.0	0.56
Arthropathy onset in relation to IBD diagnosis			
• CBP	84% after/16% before	-	
• pJTC	80% after/20% before	-	
Arthropathy onset *after* IBD diagnosis (years)			
• CBP in CD(n=46)/UC(n=17)	14.7 ± 12.6/17.8 ± 10.5 (ns)	-	
• pJTC in CD(n=86)/UC(n=26)	11.6 ± 10.5/13.0 ± 9.6 (ns)	-	
Smoker, n (%)	47 (30.0)	13 (13.0)	0.001
Montreal classification			
Location CD, n (%)	*n=121*	*n=65*	0.06
L1 ileal	34 (28.1)	12 (18.5)	
L2 colonic	27 (22.3)	13 (20.0)	
L3 ileocolonic	52 (43.0)	31 (47.7)	
L4 upper	-	2 (3.1)	
L1-3+L4	8 (6.6)	7 (10.8)	
Behaviour CD, n (%)			0.07
B1 non-structuring/penetrating	77 (63.6)	32 (49.2)	
B2 structuring	24 (19.8)	14 (21.5)	
B3 penetrating	20 (16.5)	19 (29.2)	
+ Perianal disease	37 (30.6)	18 (27.7)	
Extension UC, n (%)	*n=34*	*n=35*	0.23
E1 ulcerative proctitis	5 (14.7)	2 (5.7)	
E2 left sided UC	13 (38.2)	10 (28.6)	
E3 extensive UC (pancolitis)	16 (47.1)	23 (65.7)	
IBD-related surgery, n (%)	68 (43.9)	39 (39.0)	0.44
Family history SpA, [a] n (%)	45 (29.0)	29 (29.0)	1.0
Extra-intestinal manifestations, [b] n (%)			
Skin	27 (17.4)	7 (7.0)	0.04
Eye	22 (14.2)	5 (5.0)	0.02
Current medication use, n (%)			
5-ASA (mesa, sulfa)	24 (15.5)	27 (27.0)	0.03
Steroids	11 (7.1)	3 (3.0)	0.16
Immunosuppressive drugs (Aza/6MP/MTX)	34 (21.9)	21 (21.0)	0.86
Anti-TNF	42 (27.1)	30 (30.0)	0.61
None	44 (28.4)	19 (19.0)	0.09

[a] Family history SpA: AS, reactive arthritis, psoriasis, IBD, uveitis all according to the definition of the ASAS criteria;
[b] Skin: psoriasis, erythema nodosum, pyoderma gangrenosum. Eye: acute anterior uveitis.

Table 2. Characteristics of 155 IBD patients with self-reported joint and/or back pain.

	Chronic Back Pain (n=13)	Peripheral joint complaints (n=80)	Both (n=62)	P-value
Type of IBD, n (%)				0.61
Crohn's disease	10 (76.9)	65 (81.3)	46 (74.2)	
Ulcerative colitis	3 (23.1)	15 (18.8)	16 (25.8)	
Male, n (%)	6 (46.2)	21 (26.3)	19 (30.6)	0.34
Age at inclusion (years), mean ± SD	38.2 ± 13.8	41.9 ± 13.5	46.2 ± 13.2	0.06
Age of IBD onset (years), mean ± SD	27.0 ± 14.0	33.0 ± 11.6	48.0 ± 13.5	0.25
IBD disease duration (years), mean ± SD	21.0 ± 19.8	33.0 ± 77.2	6.0 ± 6.7	0.21
Location (most painful) peripheral joints, n (%)				0.16
Shoulder	-	10 (12.5)	6 (9.7)	
Elbow	-	10 (12.5)	2 (3.2)	
Wrist	-	9 (11.3)	7 (11.3)	
Hand (MCP-PIP-DIPs)	-	26 (32.5)	22 (35.5)	
Hip	-	1 (1.3)	4 (6.5)	
Knee	-	14 (17.5)	17 (27.4)	
Ankle	-	6 (7.5)	1 (1.6)	
Feet	-	4 (5.0)	3 (4.8)	
Distribution, n (%)				0.22
Monoarticular	-	16 (20.0)	6 (9.8)	
Oligoarticular	-	32 (40.0)	30 (48.3)	
Polyarticular	-	32 (40.0)	26 (41.9)	
SpA features, n (%)				
Arthritis [a]	0 (0.0)	8 (10.0)	7 (11.3)	0.45
HLA-B27 positive (n=150)	0 (0.0)	1 (1.3)	6 (9.7)	0.15
Positive family for SpA	5 (38.5)	20 (25.0)	18 (29.0)	0.59
Inflammatory Back Pain	5 (38.5)	-	37 (59.7)	0.001
Psoriasis [a]	2 (15.4)	7 (8.8)	5 (8.1)	0.71
Dactylitis [a]	0 (0.0)	1 (1.3)	0 (0.0)	0.62
Enthesitis [a]	0 (0.0)	0 (0.0)	1 (1.6)	0.47
Uveitis [a]	1 (7.7)	10 (12.5)	9 (14.5)	0.78
Preceding infection	0 (0.0)	0 (0.0)	0 (0.0)	-
Alternating buttock pain	3 (23.1)	0 (0.0)	22 (35.5)	0.001
Good response to NSAIDs (n=44)	2 (15.4)	20 (25.0)	11 (17.7)	0.57
Sacroiliitis on radiograph	1 (7.7)	0 (0.0)	4 (6.5)	0.06
Sacroiliitis on MRI (n=0)	-	-	-	-
Total SpA features, n (mean)	22 (1.7)	108 (1.4)	141 (2.3)	
Patients classified with SpA [b], n (%)	6 (46.2)	14 (17.5)	43 (69.4)	0.001
Elevated CRP, n (%)	1 (7.7)	15 (18.8)	11 (17.7)	0.64
Elevated ESR (n=153), n (%)	2 (15.4)	26 (32.5)	10 (16.1)	0.60

[a] All confirmed by a specialist; [b] Based on one of the different SpA criteria.

Table 3. Logistic regression analyses of IBD patients, with the presence of arthropathies as the dependent variable.

		Univariate		Multivariate	
Variable	**n**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Age (years) visit 1	255	1.0 (0.99-1.02)	0.71	-	
Gender					
Male	97				
Female (ref)	158	2.47 (1.46-4.16)	0.001	1.97 (1.10-3.53)	0.02
Type of IBD					
UC	69				
CD (ref)	186	1.92 (1.10-3.36)	0.02	1.25 (0.66-2.35)	0.51
Smoking					
No	195				
Yes (ref)	60	2.91 (1.48-5.73)	0.002	2.28 (1.10-4.75)	0.03
Active IBD disease [a]					
No	153				
Yes (ref)	103	4.61 (2.57-8.26)	<0.001	4.07 (2.23-7.45)	<0.001
IBD-related surgery					
No	148				
Yes (ref)	107	1.22 (0.73-2.04)	0.44		
Cutaneous manifestations [b]					
No	221				
Yes (ref)	34	2.80 (1.17-6.71)	0.02	1.74 (0.66-4.56)	0.26
Ocular manifestation [c]					
No	228				
Yes (ref)	27	3.14 (1.15-8.6)	0.03	1.83 (0.61-5.48)	0.28
Family history SpA [d]					
No	181				
Yes (ref)	74	1.0 (0.57-1.74)	1.00		

[a] HBI or SCCAI score > 4; [b] Cutaneous manifestations: psoriasis, erythema nodosum, pyoderma gangrenosum; [c] Ocular manifestation: acute anterior uveitis; [d] Family history SpA (SpondyloArthritis); ankylosing spondylitis, reactive arthritis, psoriasis, IBD, uveitis all according to the definition of the ASAS criteria.

Figure 1. Patient inclusion flow chart.

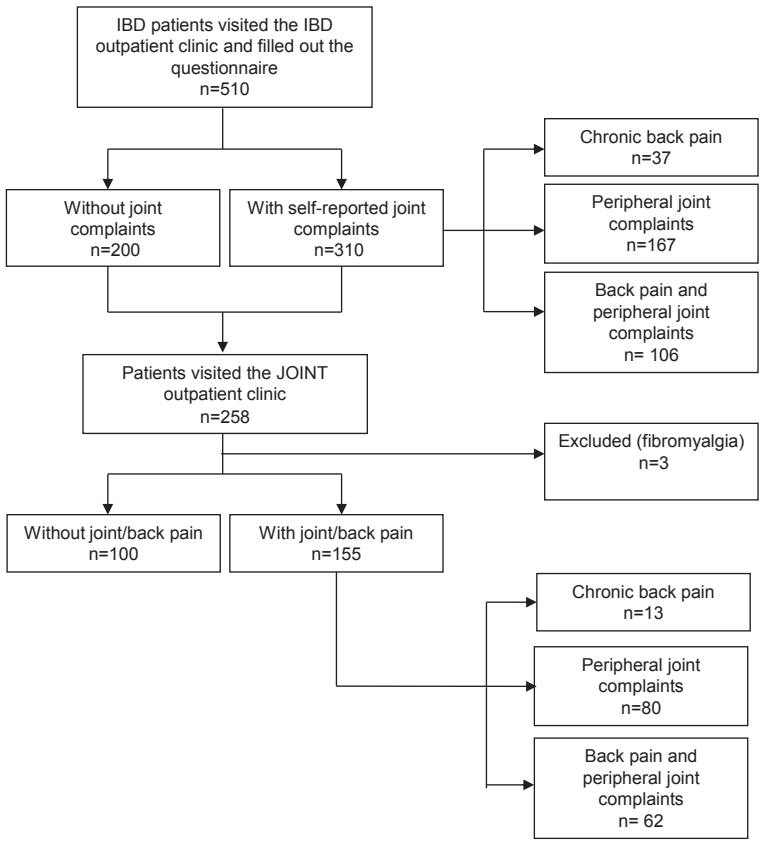
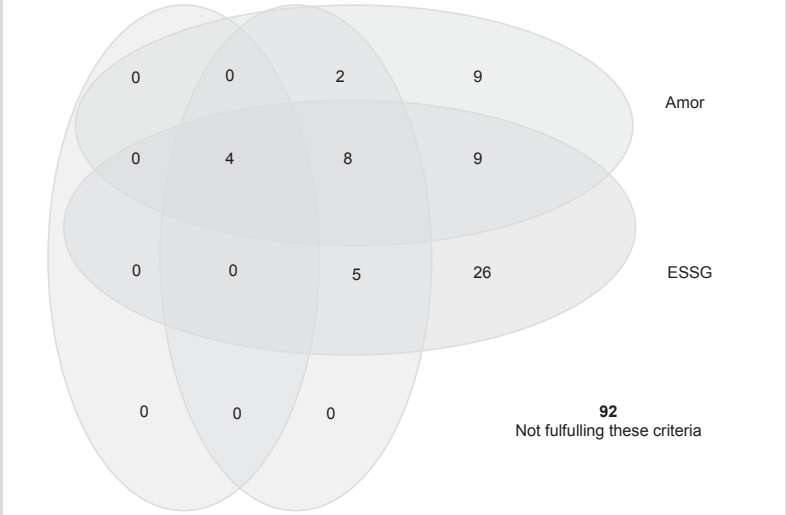


Figure 2. Venn diagram representing the overlap between the various classification criteria for SpA.



Patients were classified as SpondyloArthritis (SpA) according to the Amor[15], European Spondyloarthropathy Study Group (ESSG)[16], Assessment of SpondyloArthritis international Society (ASAS) (axial and peripheral SpA)[17-18] and modified New York (mNY) criteria.[19]

Figure 3. Follow-up IBD patients.

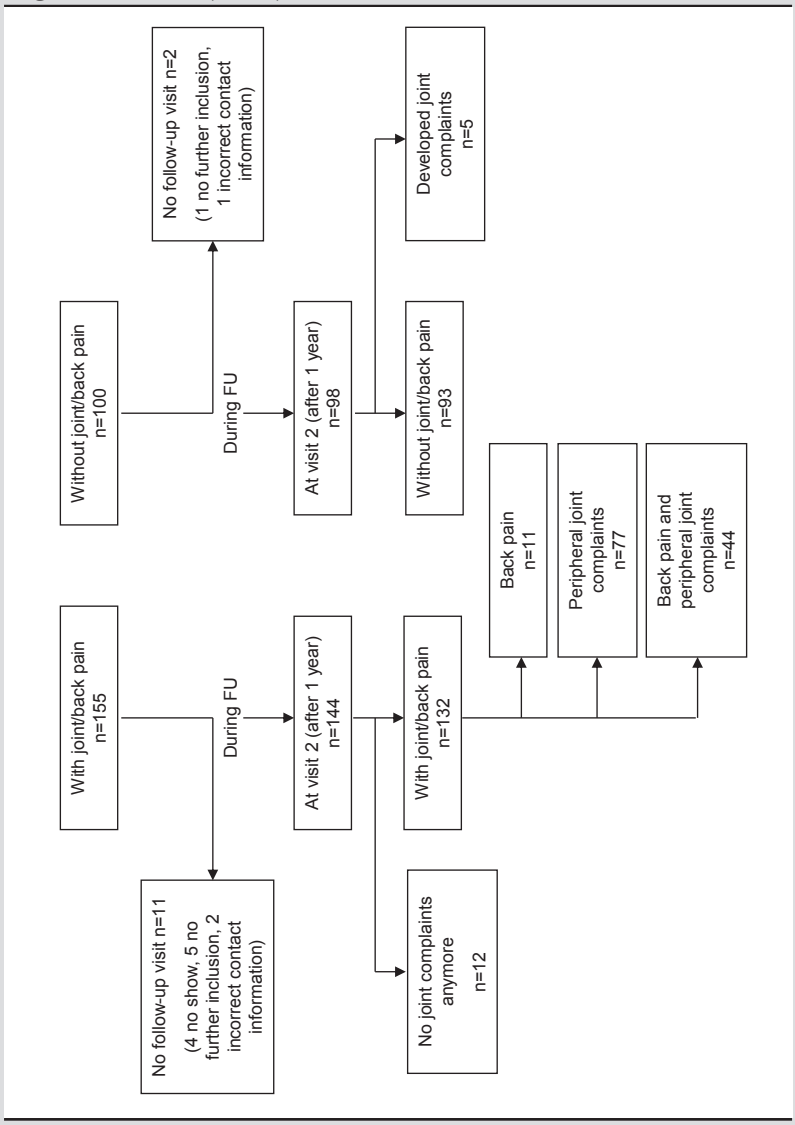
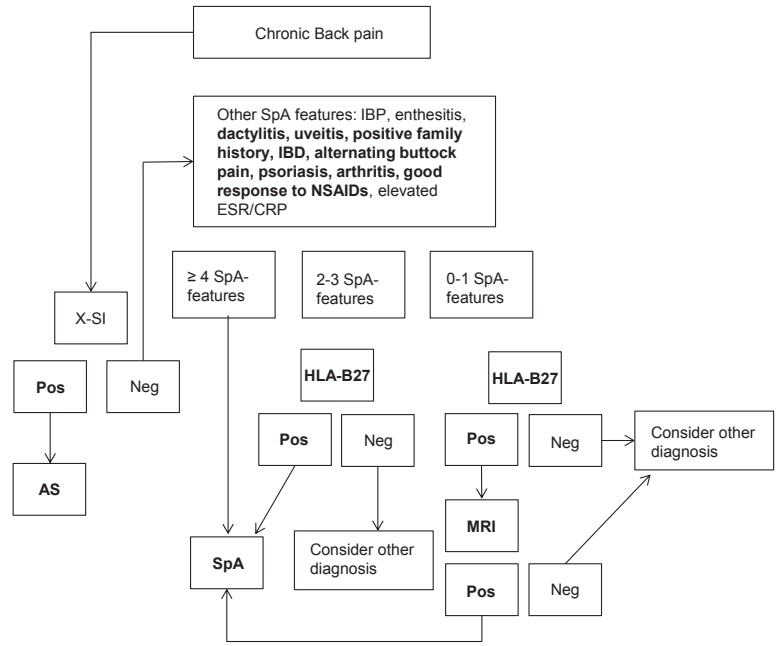


Figure 4. Proposal for the referral algorithm for suspected axial SpA in patients with IBD.



The first step for the gastroenterologist is to refer all patients with CBP to the radiologist to examine whether sacroiliitis can be found on the anterior-posterior (AP) plain radiograph of the pelvis. Conventional radiography of the SI joints is recommended as first imaging method, but in certain cases, such as young patients and those with a short symptom duration, MRI is an alternative as first method.[38] The patients with an indicated sacroiliitis on the radiograph, should be referred to the rheumatologist. In patients who are not positive for sacroiliitis of the pelvis, the presence of different SpA features should be ascertained. A patient with ≥ 4 SpA features should be referred to the rheumatologist and has a high probability of having axial SpA. Patients with fewer than four SpA features should undergo HLA-B27 testing. Patients with a positive HLA-B27 test and 2-3 SpA features possibly have axial SpA and thus will be referred to the rheumatologist. Patients with a positive HLA-B27 test and the presence of ≤ 1 SpA feature should undergo MRI.[31]