Data from a multicentric international study unveils a neglected association between chronic non-bacterial osteomyelitis and inflammatory bowel diseases

C. Matucci-Cerinic[1,2], Y. Bayindir[3], C. Longo[4], F. Mori[2], F. Alessi[2], M. Vergani[5], S. Rosina[2], A. Consolaro[1,2], S. Volpi[1,2], R. Caorsi[1,2], S. Arrigo[4], M. Gattorno[2], S. Ozen[3], C. Malattia[1,2]

[1]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Mother-child Health - DINOGMI, University of Genova; [2]UOC Rheumatology and Autoinflammatory Diseases, IRCCS Istituto Giannina Gaslini, Genova, Italy; [3]Department of Paediatric Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey; [4]Paediatric Gastroenterology and Endoscopy, and [5]Clinical Bioinformatics, IRCCS Istituto Giannina Gaslini, Genova, Italy.

Abstract

Objective

We aimed to evaluate the clinical, serological, radiological characteristics and response to treatments of patients with chronic-non-bacterial-osteomyelitis (CNO) associated with inflammatory bowel diseases (C-IBD) in comparison to CNO patients without gastrointestinal disease.

Methods

Patients with C-IBD followed in the Rheumatology Department of the Istituto Gaslini, Genova, and Hacettepe Hospital, Ankara, were retrospectively enrolled in the Eurofever Registry and compared to a group of CNO patients. A literature review on paediatric C-IBD was also performed.

Results

19 C-IBD patients were compared to 57 CNO. In C-IBD, disease onset was characterised by osteoarticular symptoms in 73.6%, by gastrointestinal symptoms in 10.5%, and was simultaneous in 15.8%. Spinal involvement was more frequent in CNO ($p<0.05$), while sacroiliac involvement was more frequent in C-IBD ($p<0.005$). 42% of C-IBD presented low-grade fever ($p<0.05$, 15% of CNO). All C-IBD presented a CRP elevation, present in only 45% of CNO ($p<0.0001$). In 68.4% of C-IBD, CRP remained elevated and became negative only after IBD treatment was started. Moreover, 58% of C-IBD patients presented microcytic anaemia (present in 17.6% CNO, $p=0.0005$). Fecal calprotectin resulted positive in 100% of C-IBD and 10% of CNO ($p<0.0001$).

Conclusion

This is the largest cohort of paediatric C-IBD reported in the literature. The persistence of inflammation and the presence of microcytic anaemia were associated with the development of an IBD. Given the frequent absence of intestinal symptoms, screening with fecal calprotectin is suggested in all CNO patients that present a persistent CRP elevation despite treatment, and have microcytic anaemia.

Key words

chronic non-bacterial osteomyelitis, chronic recurrent multifocal osteomyelitis, inflammatory bowel disease, Crohn, ulcerative colitis

Caterina Matucci-Cerinic, MD
Yagmur Bayindir, MD
Chiara Longo, MD
Francesco Mori, MD
Francesca Alessi, MD
Matteo Vergani, MSc
Silvia Rosina, MD, PhD
Alessandro Consolaro, MD, PhD
Stefano Volpi, MD
Roberta Caorsi, MD
Serena Arrigo, MD
Marco Gattorno, MD
Seza Ozen, MD
Clara Malattia, MD

Please address correspondence to:
Caterina Matucci-Cerinic
UOC Reumatologia e Malattia Autoinfiammatorie,
IRCCS Istituto Giannina Gaslini,
Via G. Gaslini 5,
16147 Genova, Italy
E-mail: c.matuccicerinic@gmail.com
ORCID iD: 0000-0003-3710-0569

Received on March 14, 2025; accepted in revised form on May 15, 2025.

Competing interests: none declared.

Introduction

Chronic non-bacterial osteomyelitis (CNO), is an autoinflammatory disease characterised by episodes of inflammatory non-infectious osteomyelitis primarily affecting children and adolescents. Its clinical presentation is very heterogeneous, ranging from focal monostotic involvement, to a more severe multifocal, chronic relapsing disease, for which it is also known as chronic recurrent multifocal osteomyelitis (CRMO) (1). CNO has a peak age onset between 9 and 11 years of age (2) and its prevalence is of 0.4–1 per 100,000 (3, 4), with a slight predilection for females. CNO is characterised by a sterile bone inflammation typically involving the meta-epiphysis of the long bones, the axial skeleton, and in some cases the anterior chest wall, especially the clavicle, and the mandible (5). Also, enthesitis and arthritis can occur.

Whole-body MRI (WB-MRI) is the most sensitive diagnostic tool for an early detection of bone marrow oedema before the appearance of the typical osteosclerotic modifications on x-ray (6). Furthermore, WB imaging recognises the patterns of bone involvement (*e.g.* bilateral, symmetric multifocal pattern or clavicle, pauci-axial pattern) and may also define the lesion severity (*e.g.* vertebral collapse).

No evidence-based guidelines for the treatment of CNO exist, with non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate, salazopyrin, bisphosphonates and anti-tumour necrosis factor (anti-TNF) drugs being the most used with different outcomes (7).

Diagnostic criteria for children have been proposed by Jansson *et al.* and by the Bristol group (8, 9). These criteria bear a superposition with the adult SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis) syndrome criteria (10), which can be interpreted as the same disease as CNO in adults.

CNO can be associated to a wide variety of skin manifestations that range from psoriasis vulgaris to palmoplantar pustulosis, acne, pyoderma gangrenosum, hidradenitis suppurativa and Sweet syndrome (11, 12).

In 1992, an association between CNO and IBD was reported by Kahn *et al.* in a case series (13), and afterwards in an increasing number of case reports has been reported. Yet, the link between bone and gut is unclear. A link between IBD and osteoarticular manifestations has been suggested through the gut-joint axis (14). It is also worth noting that the alteration of the oral and fecal microbiome of CNO patients compared to healthy controls (15) may suggest a role of intestinal dysbiosis in the disease pathogenesis. Recently, a literature review identified 57 adult and paediatric CNO cases with associated IBD, but the clinical features were very heterogeneous (16).

Therefore, the aim of our study was to report on a large cohort of CNO patients with associated IBD (C-IBD), to describe their clinical, radiological, serological features, and also provide the therapeutic response. These C-IBD patients were compared to a cohort of CNO patients without intestinal involvement to understand the main clinical differences characterising the two cohorts and also the differences in disease evolution and response to treatments.

Methods

Patients, retrospectively recruited from the Istituto Giannina Gaslini, Genova, Italy, and from the Hacettepe University Hospital, Ankara, Turkey, fulfilled the Jansson's and the Bristol's criteria for CNO (8, 9). The C-IBD patients were diagnosed as IBD and classified into Crohn's disease (CD), Ulcerative Colitis (UC) and Undifferentiated-IBD (U-IBD) on the base of the ESPGHAN Revised Porto criteria for IBD (17). The disease onset for all patients was before 18 years of age.

The C-IBD patients were compared to a randomly selected CNO cohort provided by the same centres, with a proportion of 1:3.

The demographic, clinical, laboratory, radiological features and response to treatments of the enrolled patients were retrospectively analysed.

All patients were enrolled in the Eurofever Registry, whose main characteristics have been previously described (18, 19). The study was approved by the Ethical review board of Regione Liguria. All patients gave their written

Table I. Demographic and clinical characteristics of the 2 cohorts.

	C-IBD n=19	CNO n=57	*p*-value
Male/female	12/7	22/35	NS
Age onset CNO, years, median (IQR)	10.48 [7.9;12.3]	9.17 [8.4; 10.9]	NS
Age diagnosis CNO years, median (IQR)	11.75 [8.9; 13.4]	10.66 [8.8; 12.2]	NS
Age onset IBD, median (IQR)	12.1 [8.4; 13.5] (3 patients no GI symptoms)		
Age diagnosis IBD, median (IQR)	12.03 [10.3; 13.9]		
1st symptom CNO, n (%)	14 (73.7)		
Time CNO onset-IBD onset (years, mean)	1.9		
1st symptom IBD, n (%)	2 (10.5)		
Time IBD onset-CNO onset (years, mean)	2.13		
Simultaneous onset, n (%)	3 (15.8)		
Familiarity, n	2 IBD, 1 PsA 2 IBD, 2 AIT, 1 DM1, 1 vitiligo	4Pso, 5PsA, 1AS, 1 SAPHO, 2 RA,	
Comorbidities	2 SC and AIH, 1 Pso and PG 1 FMF (MEFV M694V homozygous)	3 coeliac disease, 2 severe acne	
Clinical manifestations			
Fever, n (%)	8 (42.1)	8 (14.0)	<0.05
Osteoarticular pain, n (%)	18 (94.7)	56 (98.2)	NS
Arthritis, n (%)	8 (42.1)	9 (15.7)	<0.05
Enthesitis, n (%)	0	1 (1.7)	NS
Axial & peripheral involvement, n (%)	13 (68.4)	38 (66.7)	NS
Only peripheral involvement, n (%)	5 (26.3)	11 (19.3)	NS
Only axial involvement, n (%)	1 (5.3)	8 (14.04)	NS

AIH: autoimmune hepatitis; AIT: autoimmune thyroiditis; AS: ankylosing spondylitis; DM1: diabetes mellitus type 1; IBD: inflammatory bowel disease; NS: not significant; PsA: psoriatic arthritis; Pso: psoriasis; RA: rheumatoid arthritis; SAPHO: syonovitis-acne-pustulosis-hyperostosis-osteitis; SC: sclerosing cholangitis.

consent to be included in the registry and for publication.

Literature review

A literature review regarding the coexistence of CNO and IBD in paediatric patients was performed. The research was conducted on Pubmed until September 2024, using the key words 'pediatric', 'SAPHO syndrome', 'CRMO', 'CNO' AND 'inflammatory bowel disease', 'Crohn', 'ulcerative colitis'. Inclusion criteria were an age onset <18 years. Data regarding age, sex, first symptom at disease onset, inflammatory biomarkers and osteoarticular involvement were collected. Articles with missing information were excluded. A comparison of the literature cohort with our cohort of C-IBD patients was then conducted.

Statistical analysis

Descriptive statistics are reported as absolute frequencies and percentages for categorical variables and as median values with first and third quartiles (1st–3rd q) for continuous data. Missing values were assigned to those patients with different values from 0/1 classification used for binary variables. Comparison of frequencies between groups was performed by the means of the Chi-square test or by the Fisher's exact test in case of expected frequencies less than 5. All statistical tests were 2-sided, and *p*-values less than 0.05 were considered statistically significant. software R (v. 4.3.3) was used for descriptive analyses and bivariate analyses through the Fisher's exact test.

Results

A total of 76 CNO patients were included, 19 with an associated IBD (C-IBD) and 57 without intestinal involvement.

The demographic and clinical characteristics of the whole cohort are reported in Table I, while the gastrointestinal manifestations of the C-IBD cohort in Table II.

In the C-IBD cohort, 63% of patients (n=12) were male. The disease onset was characterised by osteoarticular symptoms in 74% (n=14), by gastrointestinal symptoms (GI) in 10% (n=2) and in 15.7% (n=3) the onset was simultaneous. The median age at CNO onset was 10.48 (7.9;12.3), while at IBD onset was 12.1 (8.4; 13.5) (Table I). In the CNO cohort, 40% of the patients were male (n=23): the median age at disease onset was 9.08 (IQR 8.35;10.98).

Table II. Gastrointestinal manifestations of the C-IBD cohort.

GI symptoms, n (%)	15 (78.9)
Abdominal pain, n (%)	9 (47.4)
Diarrhoea, n (%)	12 (63.1)
Haematochezia, n (%)	5 (26.3)
Weight loss, n (%)	7 (36.9)
IBD type, n (%)	
Crohn' disease	10 (52.6)
Ulcerative colitis	4 (21.0)
Undefined-IBD	5 (26.3)
Bowel thickening on US, n (%)	8/18 (44.4)
Positive bowel MRI, n (%)	5/9 (55.5%)

GI: gastrointestinal; IBD: inflammatory bowel disease; US: ultrasound; MRI: magnetic resonance imaging.

Systemic features

42% of C-IBD patients (n=8/19) presented with low grade fever at disease onset, which was instead present in only 15% (n=9/57) of the CNO cohort ($p<0.05$). No patients presented with uveitis.

Gastrointestinal manifestations of the C-IBD cohort

GI manifestations were the first symptom in only 2 patients (10.5%), and appeared simultaneously with osteoarticular symptoms in other 3 (15.8%). Abdominal pain was reported in 47% of patients, diarrhoea in 63%, weight

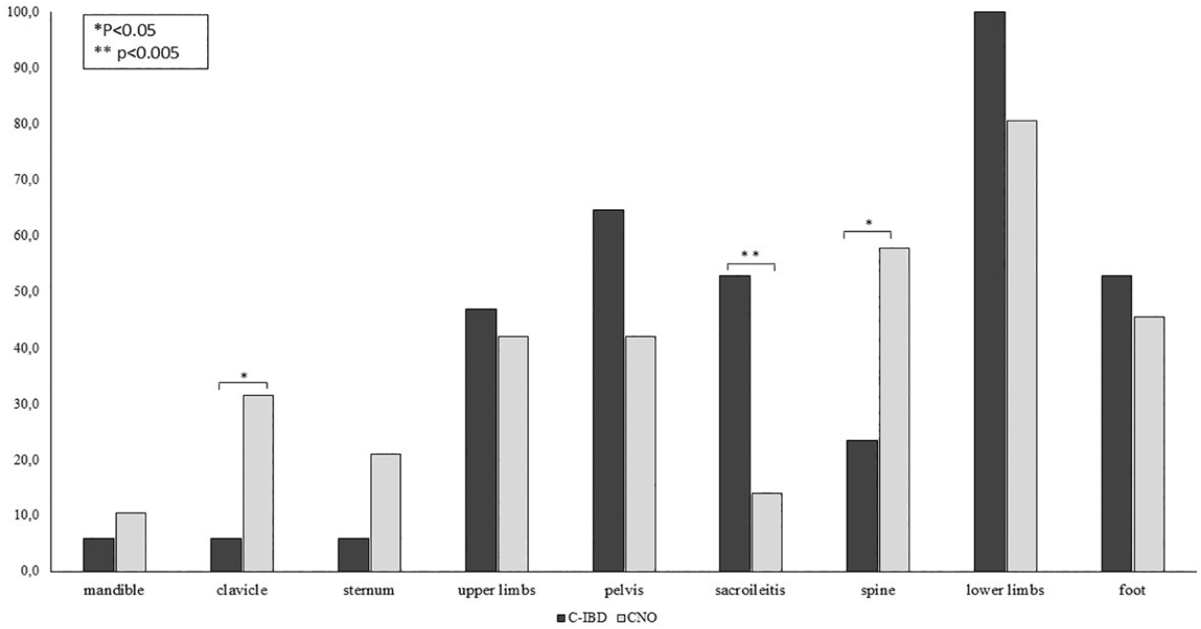

Fig. 1. Osteoarticular involvement of the two groups.

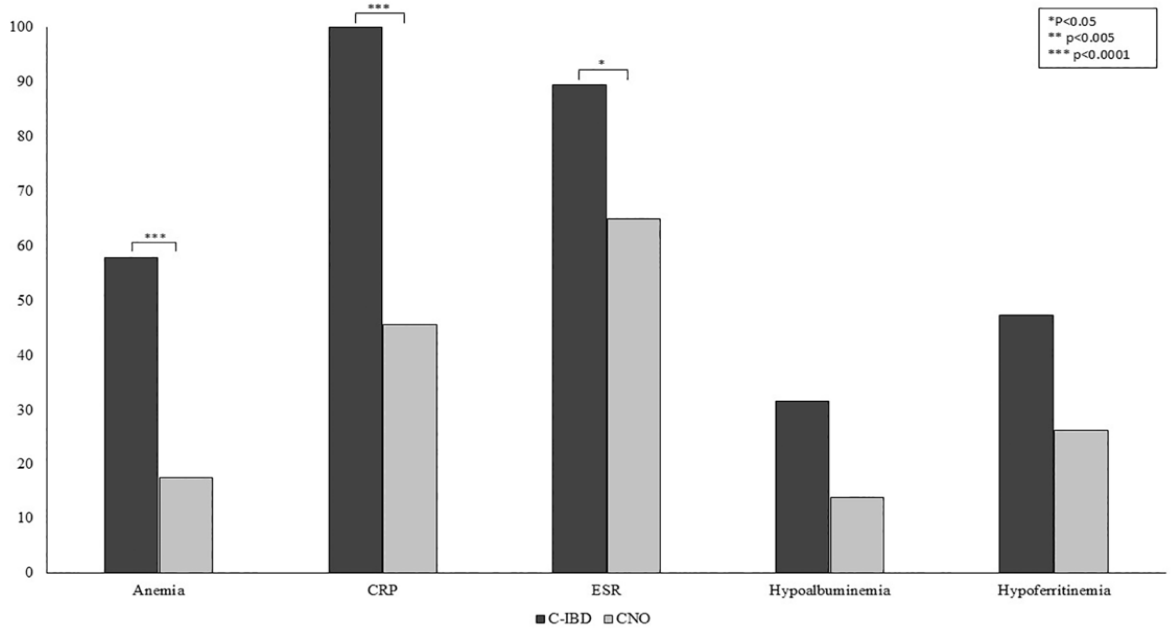

Fig. 2. Serological analysis of the two groups.
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

loss in 36% and haematochezia in 26%. Four patients (21%) were completely asymptomatic, and were investigated for an IBD due to the finding of elevated fecal calprotectin. The abdominal ultrasound (performed in 18/19 patients), was positive for a bowel thickening in 8 subjects (44.4%). A bowel MRI was performed in 9 patients, with positive results in 5 (55.5%). All patients underwent a diagnostic endoscopic procedure (gastroscopy and coloscopy), that allowed the diagnosis of CD in 10 patients (52.6%), UC in 4 (21%), and U-IBD in 5 patients (26.3%). One patient with CD developed a rectal fistula.

Osteoarticular manifestations

All patients underwent a total-body MRI: the osteoarticular involvement of the two groups is reported in Figure 1. Six patients (31.6%) of the C-IBD and 38 patients (66.6%) of the CNO group underwent a bone biopsy which showed a sterile inflammatory bone lymphocytic infiltrate.

In both cohorts, patients presented osteoarticular pain, which was associated with arthritis in 8 patients (42.1%) of the C-IBD cohort and in 9 patients (15.7%) of the CNO group ($p<0.05$). Enthesitis was present only in one patient with CNO (1.7%).

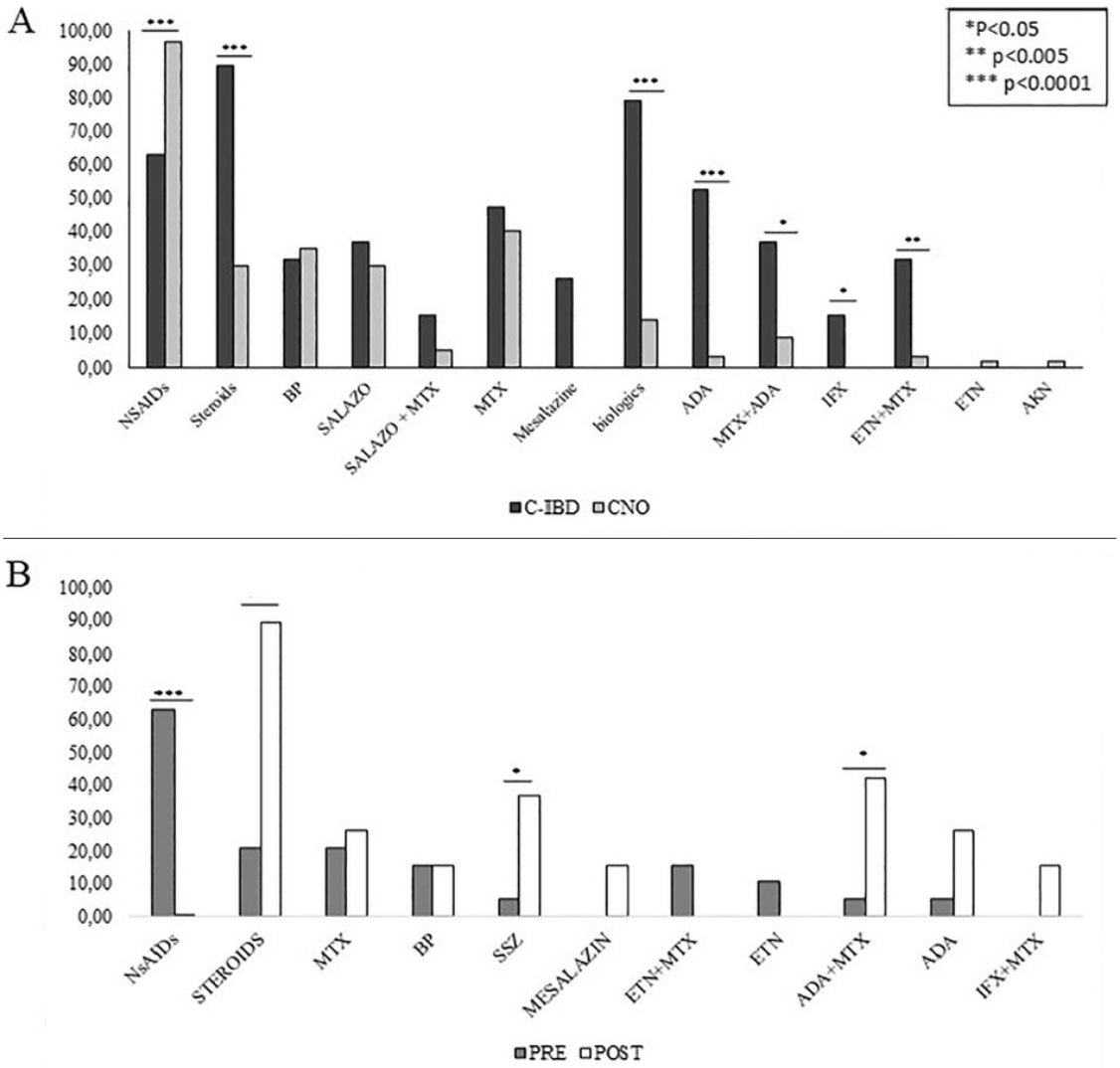

Fig. 3. **A**: Treatments used in the two cohorts. **B**: Treatments used in C-IBD cohort before and after IBD diagnosis.

The mandible and clavicle were more frequently affected in the CNO group, even if only the clavicle involvement, present in 31.9% of CNO and 5.9% of C-IBD resulted statistically significant (p=0.05). An axial involvement was present in both groups, even if sternal (CNO 21.1% *vs*. C-IBD 5.9%) and spinal (CNO 57.9% *vs*. C-IBD 23.5%) involvement were more frequently associated to CNO patients, with spinal involvement resulting statistically significant (p<0.05). Conversely, the C-IBD group exhibited a higher frequency of sacroiliac (C-IBD 52.9% *vs*. CNO 14%, p<0.005) and pelvic (C-IBD 64.7% *vs*. CNO 42.1%) involvement.

Laboratory work-up

The principal laboratory differences between the two groups are shown in Figure 2. The C-IBD showed a statistically significant major prevalence of microcytic anaemia, which was present in 64.7% of C-IBD and in only 17.6% of CNO (p=0.0005). Hypoalbuminaemia and hypoferritinaemia were more frequent in C-IBD (31.7% and 47.4% respectively, *vs*. 19.0% and 26.3% in CNO), without however reaching a statistical significance.

All the C-IBD patients (100%) presented a significative elevation of C-reactive protein (CRP) at disease onset, present in only 45% of the CNO patients (p=0.0001), and of ESR, present in 89.4% of C-IBD patients and in 69% of CNO (p<0.05).

In the CNO cohort, CRP normalised after treatment, while in the C-IBD cohort remained elevated after CNO diagnosis and treatment in 13 patients (68.4%), and normalised only once IBD was diagnosed and an appropriate treatment was started. In all C-IBD patients fecal calprotectin was positive, while in CNO patients was positive in 2/20 patients (p<0.0001): in these patients, colonoscopy resulted negative. None of the C-IBD patients was HLA B27 positive, which was positive in 3/19 CNO patients (15.8%, p not significant). Antinuclear antibodies were positive in 23.5% and 15.1% of C-IBD and CNO respectively (p not significant); and one C-IBD patient with associated sclerosing cholangitis tested positive for anti-neutrophil cytoplasmic antibodies.

Treatment

Figure 3A compares the treatment strategies in the two cohorts. Figure 3B shows the treatments of the C-IBD

Table III. Comparison of the C-IBD cohort with the literature cohort.

	C-IBD n=19	Literature n=41	*p*-value
Males/females	12/7	18/23	NS
Age at disease onset, median, years (IQR)	10.5 (8;12.3)	10 (9;12)	NS
1st symptom CNO, n (%)	14 (73.6)	23 (56)	NS
Age onset CNO, years, median (IQR)	10.48 (7.9;12.3)	10 (9;10.5)	NS
Time CNO onset-IBD onset (years, mean)	1.9	2.2	NS
Age onset IBD, median (IQR)	12.1 (8.4; 13.5)	9 (8;10)	NS
1st symptom IBD, n (%)	2 (10.5)	10 (24.4)	NS
Time IBD onset-CNO onset (years, mean)	2.13	3.6	NS
Simultaneous onset, n (%)	3 (15.8)	8 (19.5)	NS
IBD type, n (%)			
Crohn' disease	10 (52.6)	24 (58.5)	NS
Ulcerative colitis	4 (21.0)	15 (36.6)	NS
Undefined-IBD	5 (26.3)	2 (4.9)	0.02
Elevated ESR, n/tot (%)	17 (89.4)	24/25 (96)	NS
Elevated CRP, n/tot (%)	19 (100)	16/18 (88.8)	NS
Anaemia, n/tot (%)	11/17 (64.7)	11/17 (64.7)	NS
Axial & peripheral involvement	13 (68.4)	17/39 (43.5)	NS
Only axial involvement	5 (26.3)	3/39 (7.7)	NS
Only peripheral involvement	1 (5.3)	19/39 (48.7)	0.001

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IBD: inflammatory bowel disease.

cohort before and after IBD diagnosis. NSAIDs were initially used in 60% of C-IBD patients and were the first treatment in 96% of the CNO patients (p=0.0005). At disease onset, a steroid cycle was given in 29.8% of CNO and in 21% of C-IBD patients. However, after IBD diagnosis, steroids were necessary in 89% of C-IBD patients (p<0.0001). Among conventional disease-modifying anti-rheumatic drugs, methotrexate (MTX) and salazopyrin (SSZ), were used equally in the two groups, even if SSZ was specifically added in C-IBD patients after IBD diagnosis (p=0.01). Also, the combination MTX + SSZ was slightly more frequent in the C-IBD group (C-IBD 15.8% *vs*. CNO 5.2%, p not significant). Bisphonates (BP) were added in 31.6% of C-IBD and 35% of CNO patients. C-IBD patients required more frequently the addition of a biologic therapy (C-IBD 78.9% *vs*. CNO 14% p<0.001), especially after IBD diagnosis. Among biologics, adalimumab (ADA) and ADA+MTX were most frequently used in both groups (C-IBD 52.6% and 36.8% and CNO 3.5% and 8.7% respectively, ADA p<0.0001 and ADA+MTX p=0.01). Etanercept (ETN) and ETN+MTX were initially used in 10.5% and 31.5% of C-IBD patients respectively and were discontinued after IBD diagnosis, while were used in 7% and 3% of CNO patients. Infliximab associated to MTX was used in 15.7% of the C-IBD cohort after IBD diagnosis.

Literature review

In Table III the aggregated data of the literature review are provided, while in Supplementary Table S1 the details of each article are reported.

49 cases of paediatric patients with CNO and IBD were retrieved from the literature (not considering our cases) (20-43). 8 cases (8, 44, 45) were excluded from the analysis because of lacking information.

In the literature cohort, the male:female ratio was 0.7, with a disease onset characterised in 23 patients by CNO (56.1%), in 10 by IBD (24.4) and simultaneous in 8 cases (19.5%). The age at disease onset (median 10 years, IQR 9;12) was superposable to our cohort, as was the time lag before the appearance of the second symptom.

The frequency of CD was comparable to our cohort, UC was slightly more frequent in the literature cohort (36.6% *vs*. 21%) while IBD-U was significantly more frequent in our cohort when compared to the literature (26.3% *vs*. 4.9%, p=0.02). Similarly to our cohort, an ESR and CRP elevation was present in the majority of patients reported in the literature.

Concerning bone involvement, the literature cohort presented a percentage of patients with both an axial and peripheral involvement similar to our cohort (literature 43.5% *vs*. C-IBD 48.7%), an isolated axial disease was more frequent in our cohort (C-IBD 26.3% *vs*. literature 7.7%), while an exclusive peripheral involvement was significantly more frequent in the literature cohort (C-IBD 5.3% *vs*. literature 48.7%, p=0.001).

Discussion

Our data have been obtained from the largest cohort of CNO patients with associated IBD provided up to now in the literature. The comparison of C-IBD with CNO patients without intestinal involvement has allowed us to highlight their serological and osteoarticular characteristics. Specifically, a persistent CRP elevation despite treatment, and the presence of microcytic anaemia, were the most important markers of IBD development. Also, C-IBD patients presented a statistically more significant frequency of sacroiliac involvement when compared to CNO patients, who instead had a more frequent clavicle and spinal involvement.

Approximately 50% of children diagnosed with IBD develop an extra-intestinal symptom, among which the most common is the osteoarticular involvement, which may present as oligoarthritis, enthesitis or axial disease (46). The association of IBD with an inflammatory osteitis was suggested in 1989 by Chamot *et al*. (47) when describing patients with SAPHO syndrome, and in the following years was further described by the same authors that focused on the association between inflammatory enterocolopathies and SAPHO (13). Since then, it has been ascertained that SAPHO, an inflammatory sterile osteitis, can be associated with IBD. Currently, CNO is the term used to design the same osteitis, but in children. Nevertheless, the paucity of literature on the subject is striking, with only a handful of reports discussing the association between IBD and CNO in paediatric age. In 2015, Audu *et al*. reported 3 C-IBD patients and reviewed the literature highlighting 15 paediatric and 9 adult cases, without however taking into account the adult

literature on SAPHO syndrome (22). In 2021 Dushnicky *et al*. reported 7 cases of C-IBD (27), and more recently, a literature review identified 57 patients (both adults and children) with CNO and IBD (16).

Previous studies have reported a high incidence of IBD in axial SpA (5–10%) (14), along with subclinical intestinal inflammation in the majority of SpA patients (50–60%) (14, 48). Similar results were reported in juvenile SpA (49, 50). Interestingly, also a subclinical joint inflammation in patients with IBD was reported in a study in which 15% of the IBD patients were retrospectively found to have erosive sacroiliac changes (51).

Our data highlight a prevalent sacroiliac and pelvic involvement in C-IBD when compared to CNO patients without intestinal involvement. This is in line with what reported in the initial reports of SAPHO patients with IBD (13). This characteristic and the association with skin manifestations (mainly psoriasis in this reported cohort), underlines the possible and long debated link of this disease with the group of seronegative spondyloarthropathies (SpA), that are known to be associated with IBD and with the same skin manifestations that can be found in SAPHO syndrome. On the other hand, the male predominance, the higher inflammation and the sacroiliac involvement among the C-IBD patients are within the spectrum of spondyloarthropathies associated with inflammatory diseases, including inflammatory bowel disease.

In CNO, innate immune cells have an altered expression of inflammatory cytokines and chemokines, with a reduced monocyte production of the regulatory cytokine IL-10, and an elevated production of proinflammatory cytokines (IL-1β, IL-6, TNF-α) (52, 53). This could explain the response of CNO patients to anti-TNF-α agents. Certainly, the association of CNO with other inflammatory skin and intestinal diseases suggests a possible common pathogenesis.

A link between IBD and osteoarticular manifestations has been suggested through the gut-joint axis (14). As in SpA, it could be hypothesised that also in CNO, the impairment of the intestinal barrier, and an alteration of the local microbiota, could lead to a local inflammation and a systemic cytokine release that could lead to articular, and possibly bone inflammation. Nevertheless, this hypothesis does not take into account patients who suffer from an inflammatory bone disorder without concomitant gut inflammation. This suggests the possibility of a different immunopathogenic background or genetic predisposition (14). Concerning the genetic background, Morbach *et al*., have tested a small CNO population (of whom 4 patients with associated CD) for CARD15 mutations, known to be associated to CD, concluding however that CARD15 gene variants did not segregate with CNO (33).

In our cohort, the majority of patients had CNO as first symptom, with IBD manifestations appearing after 1–2 years. This is in line with the literature (Table III) (13), with the exception of some cases (Suppl. Table S1) in whom IBD was the first diagnosis (21, 23, 27, 30, 32).

In our cohort and in the literature, CD was the most prevalent IBD. Indeed, in an adult cohort of SpA, 50% of patients presented a microscopic subclinical gut inflammation and of these, half of the patients presented an exclusive involvement of the ileum. This may suggest that in SpA the gut inflammation is mostly CD-like (14, 54). Also, a meta-analysis on IBD patients reported a more frequent development of SpA in patients with CD than in UC (55).

It is striking the initial paucity of gastrointestinal symptoms in CNO patients with IBD. In our cohort, 4 patients did not present any intestinal symptom, presenting however a positive fecal calprotectine and showing a positive histology after endoscopy. The fecal calprotectine represents an important diagnostic tool in IBD, and was found to be elevated in SpA patients with subclinical gut microscopic inflammation (56). Interestingly, in a paediatric cohort of juvenile idiopatic arthritis patients, calprotectin levels resulted significantly higher in patients with enthesitis-related arthritis and, as in SpA (14), calprotectin levels were associated with disease activity (57). These findings underline the importance of a periodic fecal calprotecine screening in CNO patients.

In our C-IBD cohort, HLA B-27 resulted negative. This is in line with the data from the literature and moreover with the pathogenesis of IBD, given the lack of association of MHC class I with IBD, which is more frequently associated with MHC class II polymorphisms (58).

In our cohort, C-IBD patients presented a significative elevation of inflammatory biomarkers when compared to CNO, where it is known that an elevation of CRP may be present. Jansson *et al*. (59), reported a CRP elevation in 59% of the patients, and therefore included CRP as part of their diagnostic CNO clinical score. However, since CRP can be elevated in multiple bone diseases, the Bristol criteria suggest the execution of a bone biopsy in case of an elevation of CRP >30g/L (9).

In our cohort, CRP and ESR remained persistently high despite CNO treatment, normalising only after IBD diagnosis, whilst in CNO patients with CRP and ESR elevated at disease onset, a normalisation was seen with a specific treatment for CNO. In CNO patients, a persistent inflammatory biomarkers elevation despite treatment could therefore be a red flag for the development of an IBD. However, our results should be interpreted in light of some potential caveat as the study was retrospective and therefore not all the data were available for all patients.

In conclusion, we have presented a large cohort of CNO patients with associated IBD, highlighting their differences with CNO patients without intestinal inflammation. The persistent elevation of inflammatory biomarkers, despite CNO treatment initiation, represented an important characteristic of the C-IBD group, thus highlighting the importance of the intestinal screening, and suggesting the performance of fecal calprotectin in CNO patients characterised by persistently elevated CRP and ESR despite treatment. Further studies are needed to better understand the association between CNO and IBD, their clinical course over time and the possible therapeutic implications.

References

1. HOFMANN SR, KAPPLUSCH F, GIRSCHICK HJ *et al*.: Chronic recurrent multifocal osteomyelitis (CRMO): presentation, pathogenesis, and treatment. *Curr Osteoporos Rep* 2017; 15(6): 542-54. https://doi.org/10.1007/s11914-017-0405-9
2. SINGHAL S, LANDES C, SHUKLA R, MCCANN LJ, HEDRICH CM: Classification and management strategies for paediatric chronic non-bacterial osteomyelitis and chronic recurrent multifocal osteomyelitis. *Expert Rev Clin Immunol* 2023; 19(9): 1101-16. https://doi.org/10.1080/1744666x.2023.2218088
3. JANSSON AF, GROTE V: Nonbacterial osteitis in children: data of a German Incidence Surveillance Study. *Acta Paediatr* 2011; 100: 1150-57. https://doi.org/10.1111/j.1651-2227.2011.02205.x
4. WALSH P, MANNERS PJ, VERCOE J, BURGNER D, MURRAY KJ: Chronic recurrent multifocal osteomyelitis in children: nine years' experience at a statewide tertiary paediatric rheumatology referral centre. *Rheumatology* (Oxford) 2015; 54(9): 1688-91. https://doi.org/10.1093/rheumatology/kev013
5. HOFFMANN T, FINGER D: Chronic recurrent multifocal osteomyelitis. *J Rheumatol*. 2007; 34: 2499-500.
6. KIENINGER A, SCHÄFER JF, TSIFLIKAS I *et al*.: Early diagnosis and response assessment in chronic recurrent multifocal osteomyelitis: changes in lesion volume and signal intensity assessed by whole-body MRI. *Br J Radiol* 2022; 95(1130): 20211091. https://doi.org/10.1259/bjr.20211091
7. LIU S, TANG M, CAO Y, LI C: Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: review and update. *Ther Adv Musculoskelet Dis* 2020; 12. https://doi.org/10.1177/1759720x20912865
8. JANSSON A, RENNER ED, RAMSER J *et al*.: Classification of non-bacterial osteitis: retrospective study of clinical, immunological and genetic aspects in 89 patients. *Rheumatology* (Oxford) 2007; 46(1): 154-60. https://doi.org/10.1093/rheumatology/kel190
9. RODERICK MR, SHAH R, ROGERS V, FINN A, RAMANAN AV: Chronic recurrent multifocal osteomyelitis (CRMO) - advancing the diagnosis. *Pediatr Rheumatol Online J* 2016; 14(1): 47. https://doi.org/10.1186/s12969-016-0109-1
10. KAHN ME: Abstracts of the American College of Rheumatology 67th annual meeting and the Association of Rheumatology Health Professionals 38th annual meeting. October 23-28, 2003. Orlando, Florida, USA. *Arthritis Rheum* 2003; 48: S35-750.
11. GIRSCHICK H, FINETTI M, ORLANDO F *et al*.: The multifaceted presentation of chronic recurrent multifocal osteomyelitis: a series of 486 cases from the Eurofever international registry. *Rheumatology* (Oxford) 2018; 57(7): 1203-11. https://doi.org/10.1093/rheumatology/key058
12. MATUCCI-CERINIC C, MALATTIA C, PISTORIO A *et al*.: Skin manifestations help identifying different phenotypes of paediatric SAPHO syndrome. *Semin Arthritis Rheum* 2023; 63: 152277. https://doi.org/10.1016/j.semarthrit.2023.152277
13. KAHN MF, BOUCHON JP, CHAMOT AM *et al*.: [Chronic enterocolopathies and SAPHO syndrome. 8 cases]. *Rev Rhum Mal Osteoartic* 1992; 59(2): 91-94.
14. GRACEY E, VEREECKE L, MCGOVERN D *et al*.: Revisiting the gut-joint axis: links between gut inflammation and spondyloarthritis. *Nat Rev Rheumatol*. 2020; 16(8): 415-33. https://doi.org/10.1038/s41584-020-0454-9
15. RAUSCH P, HARTMANN M, BAINES JF, VON BISMARCK P: Analysis of the fecal and oral microbiota in chronic recurrent multifocal osteomyelitis. *Arthritis Res Ther* 2022; 24(1): 54. https://doi.org/10.1186/s13075-021-02711-8
16. COSTI S, GERMINARIO S, PANDOLFI M *et al*.: Chronic nonbacterial osteomyelitis and inflammatory bowel disease: a literature review-based cohort. *Children* (Basel) 2023; 10(3): 502. https://doi.org/10.3390/children10030502
17. LEVINE A, KOLETZKO S, TURNER D *et al*.: ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr*. 2014; 58: 795-806. https://doi.org/10.1097/mpg.0000000000000239
18. TER HAAR N, LACHMANN H, ÖZEN S *et al*.: Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. *Ann Rheum Dis* 2013; 72: 678-85. https://doi.org/10.1136/annrheumdis-2011-201268
19. TOPLAK N, FRENKEL J, OZEN S *et al*.: An international registry on autoinflammatory diseases: the Eurofever experience. *Ann Rheum Dis* 2012; 71(7): 1177-82. https://doi.org/10.1136/annrheumdis-2011-200549
20. AGHAROKH L, MAMOLA K, YU AG *et al*.: Cachexia, chorea, and pain in chronic nonbacterial osteitis and inflammatory bowel disease: a case report. *J Med Case Rep* 2023; 17: 237. https://doi.org/10.1186/s13256-023-03894-1
21. AHMED ABM, ALSALEEM BMR: Unusual manifestation of ulcerative colitis. *Case Rep Pediatr* 2019; 2019: 5163213. https://doi.org/10.1155/2019/5163213
22. AUDU G, KORNILIA N, CRESPI D, SPRAY C, EPSTEIN J: Chronic recurrent multifocal osteomyelitis and inflammatory bowel disease. *JPGN* 2015; 60(5); 586-91. https://doi.org/10.1097/mpg.0000000000000663
23. BAZRAFSHAN A, ZANJANI KS: Chronic recurrent multifocal osteomyelitis associated with ulcerative colitis: a case report. *J Pediatr Surg* 2000; 35: 1520-22. https://doi.org/10.1053/jpsu.2000.16431
24. BOUSVAROS A, MARCON M, TREEM W *et al*.: Chronic recurrent multifocal osteomyelitis associated with chronic inflammatory bowel disease in children. *Dig Dis Sci* 1999; 44(12): 2500-7. https://doi.org/10.1023/a:1026695224019
25. SUNDARAM M, MCDONALD D, ENGEL E, ROTMAN M, SIEGRIED EC: Chronic recurrent multifocal osteomyelitis: an evolving clinical and radiological spectrum. *Skeletal Radiol* 1996; 25(4): 333-36. https://doi.org/10.1007/s002560050091
26. CARPENTER E, JACKSON MA, FRIESEN CA, SCARBROUGH M, ROBERTS CC: Crohn's-associated chronic recurrent multifocal osteomyelitis responsive to infliximab. *J Pediatr* 2004; 144(4): 541-44. https://doi.org/10.1016/j.jpeds.2003.12.038
27. DUSHNICKY MJ, BEATTIE KA, CELLUCCI T *et al*. Pediatric patients with a dual diagnosis of inflammatory bowel disease and chronic recurrent multifocal osteomyelitis. *J Pediatr Gastroenterol Nutr* 2021; 73(5): 626-29. https://doi.org/10.1097/mpg.0000000000003225
28. FUJISAKI T, MATSUISHI T, KAMIZONO J, AMAMOTO M, MIZUOCHI T: Crohn's disease and chronic recurrent multifocal osteomyelitis in a Japanese boy. *Pediatr Int*. 2021; 63 (1): 115-17. https://doi.org/10.1111/ped.14370
29. KWAK S, KIM D, CHOI JS, YOON Y, KIM ES, KIM MJ: Chronic recurrent multifocal osteomyelitis associated with inflammatory bowel disease successfully treated with infliximab. *Pediatr Infect Vaccine* 2022; 29(2): 96-104. https://doi.org/10.14776/piv.2022.29.e14
30. LORENZE A, MEADOWS L, KEHINDE T, MENCHINI CB: A severe presentation of chronic non-infectious osteomyelitis associated with ulcerative colitis: a case report. *BMC Pediatr* 2020; 20(1): 304. https://doi.org/10.1186/s12887-020-02215-5
31. MAMBELLI L, GIOVANNELLI E, MAINETTI M, MARCHETTI F: From bone pain to abdominal pain: When chronic recurrent multifocal osteomyelitis is associated with ulcerative colitis. *Pediatr Neonatol* 2022; 63(5): 557-58. https://doi.org/10.1016/j.pedneo.2022.01.009
32. MARRANI E, BELLI G, SIMONINI G, TRAPANI S, CAPRONI M, LIONETTI P: SAPHO syndrome in pediatric patients with inflammatory bowel disease treated with infliximab. *Dig Liver Dis* 2018; 50(11): 1249-51. https://doi.org/10.1016/j.dld.2018.09.001
33. MORBACH H, DICK A, BECK C *et al*.: Association of chronic non-bacterial osteomyelitis with Crohn's disease but not with CARD15 gene variants. *Rheumatol Int* 2010; 30(5): 617-21. https://doi.org/10.1007/s00296-009-1029-x
34. OMIDI CJ, SIEGFRIED EC: Chronic recurrent multifocal osteomyelitis preceding pyoderma gangrenosum and occult ulcerative colitis in a pediatric patient. *Pediatr Dermatol* 1998; 15: 435-38. https://doi.org/10.1046/j.1525-1470.1998.1998015435.x
35. RAMRAJ R, CHUN C, MARCOVICI P: Chronic recurrent multifocal osteomyelitis in Crohn disease: complete resolution with anti-TNFα therapy. *J Pediatr Gastroenterol Nutr* 2018; 67(3): e57. https://doi.org/10.1097/mpg.0000000000001228
36. DE GUERRA VC, HASHMI H, KRAMER B *et al*.: a case report of Takayasu's arteritis and ulcerative colitis in a pediatric patient with chronic recurrent multifocal osteomyelitis successfully treated with infliximab: diagnostic clues in disease associations and immune dysregulation. *Case Rep Rheumatol* 2019; 2019: 8157969. https://doi.org/10.1155/2019/8157969
37. CANTARELLI E, BACCELLI F, SIMONINI G, ALVISI P: Chronic recurrent multifocal osteomyelitis associated with Crohn disease:

a potential role of exclusion diet? Comment on Starz *et al*. The modification of the gut microbiota via selected specific diets in patients with Crohn's disease. Nutrients 2021; 13: 2125. *Nutrients* 2021; 13(11): 4005. https://doi.org/10.3390/nu13114005

38. GOLDFARB A, BREITLING S, AMADASUN O, KIERNAN B, GOLD-VON SIMSON G, SAGALOWSKY ST: Chronic non-infectious osteomyelitis mimicking scurvy as the presenting sign of Crohn's disease: case report. *Front Pediatr* 2022; 10: 871993. https://doi.org/10.3389/fped.2022.871993
39. MANNERS P, ROBBINS P: Chronic recurrent multifocal osteomyelitis with Crohn's disease exacerbation and vasculitis after granulocyte colony-stimulating factor therapy. *J Clin Rheumatol*. 2000; 6: 283-90. https://doi.org/10.1097/00124743-200010000-00010
40. NG HY, GUTTMAN OR, TUCKER LB: Chronic recurrent multifocal osteomyelitis and primary sclerosing cholangitis with type 1 autoimmune hepatitis in a child with ulcerative colitis: a case report. *BMC Rheumatol* 2021; 5(1): 16. https://doi.org/10.1186/s41927-021-00186-3
41. VAN OMMEN C, DEHOORNE J, DE BAETS F, VANDE VELDE S, VAN WINCKEL M, VAN BIERVLIET S: A case of chronic recurrent multifocal osteomyelitis associated with crohn's disease. *Acta Gastroenterol Belg* 2015; 78: 240-43.
42. GIRSCHICK HJ, ZIMMER C, KLAUS G, DARGE K, DICK A, MORBACH H: Chronic recurrent multifocal osteomyelitis: what is it and how should it be treated? *Nat Clin Pract Rheumatol* 2007; 3(12): 733-38. https://doi.org/10.1038/ncprheum0653
43. KOŁODZIEJCZYK B, GAZDA A, HERNIK E *et al*.: Diagnostic and therapeutic difficulties in a patient with chronic recurrent multifocal osteomyelitis coexisting with ulcerative colitis. *Reumatologia* 2019; 57(2): 109-16. https://doi.org/10.5114/reum.2019.84817
44. VON KALLE T, HEIM N, HOSPACH T, LANGENDÖRFER M, WINKLER P, STUBER T: Typical patterns of bone involvement in whole-body MRI of patients with chronic recurrent multifocal osteomyelitis (CRMO). *Rofo* 2013; 185(7): 655-61. https://doi.org/10.1055/s-0033-1335283
45. SCHILLING F, MÄRKER-HERMANN E: [Chronic recurrent multifocal osteomyelitis in association with chronic inflammatory bowel disease: entheropathic CRMO]. (article in German) *Z Rheumatol* 2003; 62(6): 527-38. https://doi.org/10.1007/s00393-003-0526-7
46. JANG H-J, KANG B, CHOE B-H: The difference in extraintestinal manifestations of inflammatory bowel disease for children and adults. *Transl Pediatr* 2019; 8(1): 4-15. https://doi.org/10.21037/tp.2019.01.06
47. CHAMOT AM, BENHAMOU CL, KAHN MF, BERANECK L, KAPLAN G, PROST A: [Acnepustulosis-hyperostosis-osteitis syndrome. Results of a national survey. 85 cases]. (article in French) *Rev Rhum Mal Osteoartic* 1987; 54(3): 187-96.
48. LEIRISALO-REPO M, TURUNEN U, STENMAN S, HELENIUS P, SEPPÄLÄ K: High frequency of silent inflammatory bowel disease in spondylarthropathy. *Arthritis Rheum* 1994; 37(1): 23-31. https://doi.org/10.1002/art.1780370105
49. MIELANTS H, VEYS E, CUVELIER C, DE VOS M, GOEMAERE S, MAERTENS M, JOOS R: Gut inflammation in children with late onset pauciarticular juvenile chronic arthritis and evolution to adult spondyloarthropathy--a prospective study. *J Rheumatol* 1993; 20(9): 1567-72.
50. BARABINO A, GATTORNO M, CABRIA M *et al*.: 99mTc-white cell scanning to detect gut inflammation in children with inflammatory bowel diseases or spondyloarthropathies. *Clin Exp Rheumatol* 1998;16(3): 327-34.
51. CHAN J, SARI I, SALONEN D SILVERBERG MS, HAROON N, INMAN RD: Prevalence of sacroiliitis in inflammatory bowel disease using a standardized computed tomography scoring system. *Arthritis Care Res* 2018; 70(5): 807-10. https://doi.org/10.1002/acr.23323
52. HOFMANN S, KUBASCH A, ROSEN-WOLFF A *et al*.: Altered expression of IL-10 family cytokines in CRMO result in enhanced inflammasome activation. *Pediatr Rheumatol* 2015; 13(Suppl. 1). https://doi.org/10.1186/1546-0096-13-S1-O28
53. HOFMANN S, KUBASCH AS, RANGE U *et al*.: Serum biomarkers for the diagnosis of chronic recurrent multifocal osteomyelitis (CRMO). *Pediatr Rheumatol* 2015; 13(Suppl. 1). https://doi.org/10.1186/1546-0096-13-S1-O77
54. VAN PRAET L, VAN DEN BOSCH FE, JACQUES P *et al*.: Microscopic gut inflammation in axial spondyloarthritis: a multiparametric predictive model. *Ann Rheum Dis* 2013; 72(3): 414-17. https://doi.org/10.1136/annrheumdis-2012-202135
55. KARREMAN MC, LUIME JJ, HAZES JMW, WEEL AEAM: The prevalence and incidence of axial and peripheral spondyloarthritis in inflammatory bowel disease: a systematic review and meta-analysis. *J Crohns Colitis* 2017; 11: 631-42. https://doi.org/10.1093/ecco-jcc/jjw199
56. CYPERS H, VARKAS G, BEECKMAN S *et al*.: Elevated calprotectin levels reveal bowel inflammation in spondyloarthritis. *Ann Rheum Dis* 2016; 75(7): 1357-62. https://doi.org/10.1136/annrheumdis-2015-208025
57. LAMOT L, MILER M, VUKOJEVIĆ R *et al*.: The increased levels of fecal calprotectin in children with active enthesitis related arthritis and mri signs of sacroiliitis: the results of a single center cross-sectional exploratory study in juvenile idiopathic arthritis patients. *Front Med* (Lausanne) 2021; 8: .650619. https://doi.org/10.3389/fmed.2021.650619
58. GOYETTE P, BOUCHER G, MALLON D *et al*.: High-density mapping of the MHC identifies a shared role for HLA-DRB1*01:03 in inflammatory bowel diseases and heterozygous advantage in ulcerative colitis. *Nat Genet* 2015; 47(2): 172-79. https://doi.org/10.1038/ng.3176
59. JANSSON AF, MÜLLER TH, GLIERA L *et al*.: Clinical score for nonbacterial osteitis in children and adults. *Arthritis Rheum* 2009; 60(4): 1152-59. https://doi.org/10.1002/art.24402