Extraintestinal Manifestation of IBD:

Rheumatologist's point of view

Dott. Alfonso Massara
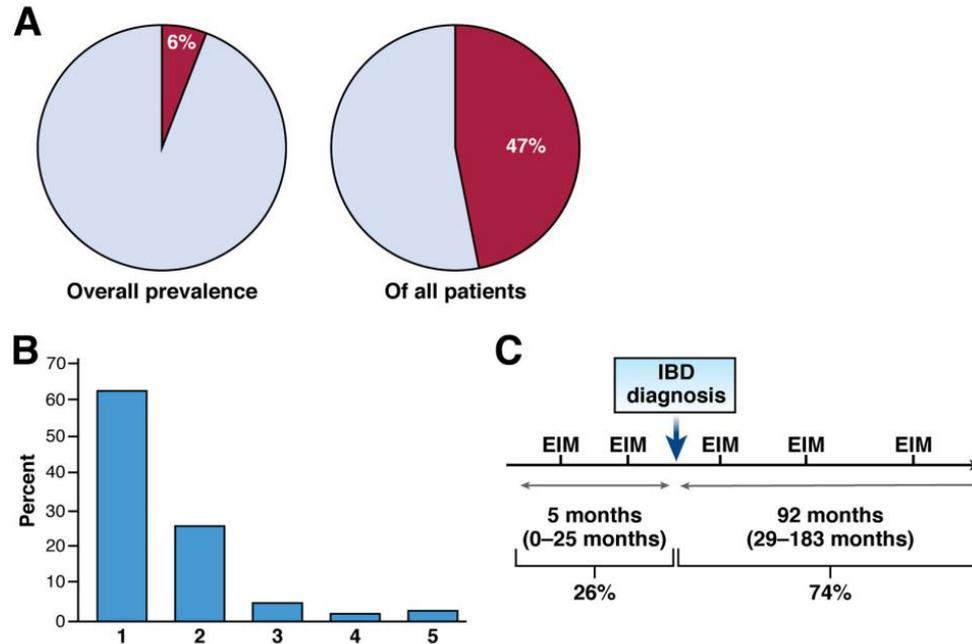**U.O.C di Reumatologia**
Azienda Ospedaliero-Universitaria, Cona

# Manifestazioni extra-intestinali delle IBD

- ➢ Impattano significativamente sulla **QoL** dei pz
- ➢ Richiedono riflessioni specifiche sulla **scelta terapeutica**
- ➢ Spesso presentano decorso **indipendente** dalla attività della malattia di base

Rogler G, *Gastroenterology* 2001

Extra-Intestinal Manifestations of Inflammatory Bowel Diseases

Organ System	Manifestations	Prevalence
Gastrointestinal	Primary sclerosing cholangitis Autoimmune pancreatitis Autoimmune hepatitis	UC: up to 5%; CD: rare rare rare (< 1%)
Mucocutaneous	Erythema nodosum Pyoderma gangrenosum Oral aphthous ulcers Sweet's syndrome Orofacial granulomatosis	5–15% in CD; 2–10% in UC 0.4 – 2.6% in IBD 5–50% in CD rare rare
Musculoskeletal	IBD-related arthritis peripheral arthritis axial arthritis enthesitis	CD: 10–20% ; UC: 4–14% Up to 50% in CD (asymptomatic)
Ocular	Episcleritis and scleritis Anterior Uveitis	Scleritis: up to 1%; CD 5–12%; UC 3.5–4.1%
Pulmonary	Pneumonitis	rare
Vascular	Cardiovascular disease Thromboembolism Portal vein thrombosis	n.a. 3–4 fold increase rare

Rogler G, *Gastroenterology* 2001

ECCO Guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease

Hannah Gordon,[a] Johan Burisch,[b] Pierre Ellul,[c] Konstantinos Karmiris,[d] Konstantinos Katsanos,[e] Mariangela Allocca,[f] Giorgos Bamias,[g] Manuel Barreiro-de Acosta,[h] Tasanee Braithwaite,[i] Thomas Greuter,[j] Catherine Harwood,[k] Pascal Juillerat,[l] Triana Lobaton,[m] Ulf Müller-Ladner,[n] Nurulamin Noor,[o] Gianluca Pellino,[p] Edoardo Savarino,[q] Christoph Schramm,[r] Alessandra Soriano,[s] Jürgen Michael Stein,[t] Mathieu Uzzan,[u] Patrick F. van Rheenen,[v] Stephan R. Vavricka,[w] Maurizio Vecchi,[x] Stephane Zuily,[y] Torsten Kucharzik[z]
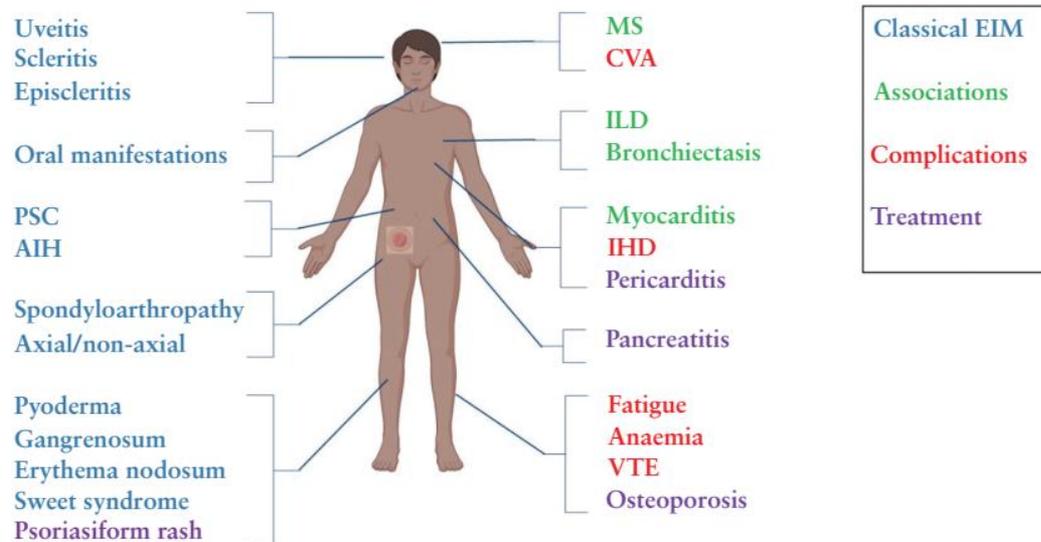
Manifestazioni osteo-articolari IBD-relate: classificazione

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- • Spondiloartrite assiale
- - *Spondiloartrite pre – (non) radiografica*
- - *Spondiloartrite radiografica (ex spondilite anchilosante)*
- • Artriti reattive
- • Artropatie IBD-relate (**SpA-IBD**)
- • Artropatia psoriasica
- • Spondiloartrite periferica
- • Spondiloartrite indifferenziata
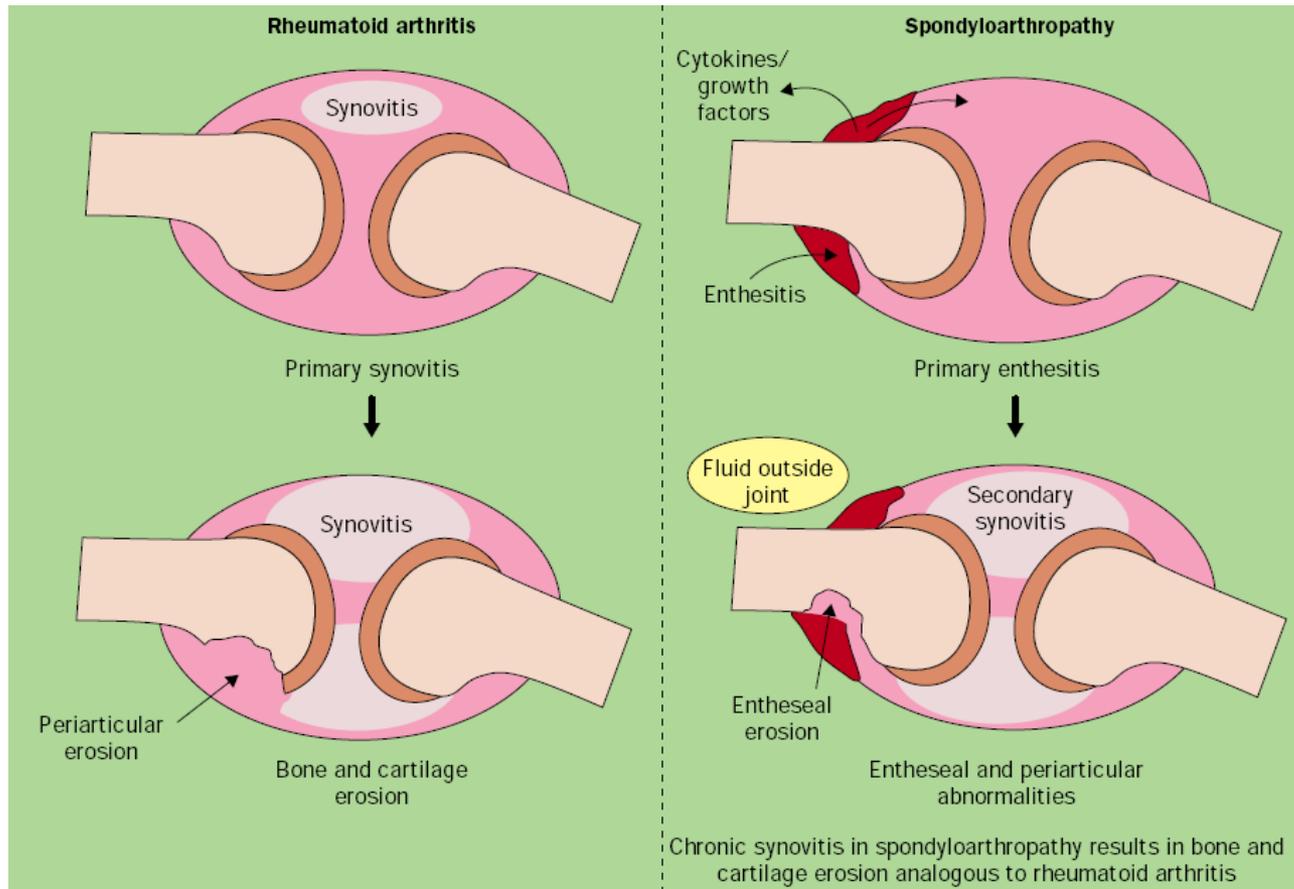
Spondilo-entesoartriti

- Coinvolgimento articolare asimmetrico, arti inferiori

- Sacroileite/Spondilite

- Entesite

- Dattilite

- Coinvolgimento delle articolazioni fibro-cartilaginee

- Assenza di fattore reumatoide e/o anti-CCP

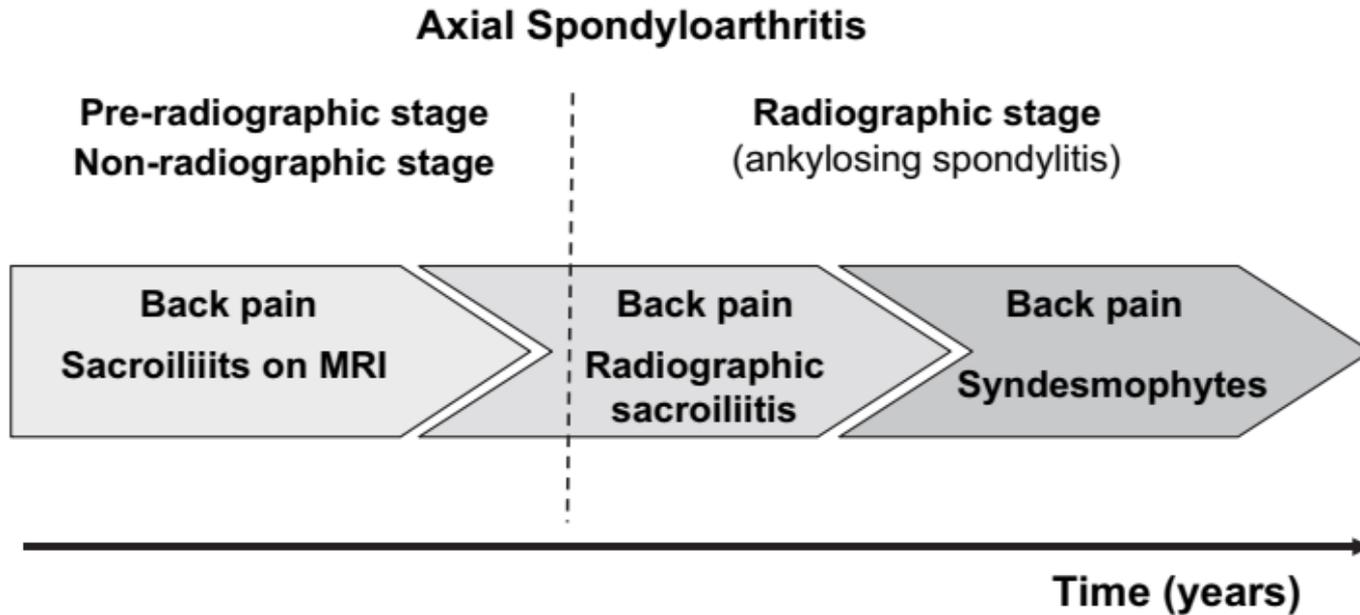- Manifestazioni extraarticolari overlapping (es. UAA)

- Familiarità (HLA-B27)

Classification of inflammatory arthritis by enthesitis

Dennis McGonagle, Wayne Gibbon, Paul Emery

Spondiloartrite assiale

Axial Spondyloarthritis

Pre-radiographic stage
Non-radiographic stage

Radiographic stage
(ankylosing spondylitis)

Back pain

Sacroiliiits on MRI

Back pain

Radiographic
sacroiliitis

Back pain

Syndesmophytes

Time (years)
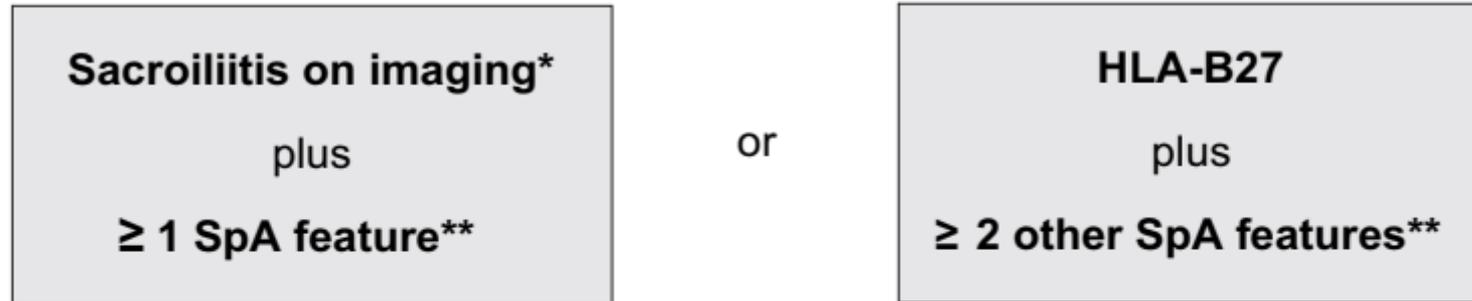
ASAS criteria 2009

ASAS classification criteria for axial SpA
(in patients with back pain ≥ 3 months and age at onset <45 years)

Sacroiliitis on imaging*

plus

≥ 1 SpA feature**

or

HLA-B27

plus

≥ 2 other SpA features**

**SpA features:
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's disease / ulcerative colitis
- Good response to NSAIDs
- Family history for SpA
- HLA-B27
- Elevated CRP

*Sacroiliitis on imaging:
- Active (acute) Inflammation on MRI highly suggestive of sacroiliitis associated with SpA

   or
- Definite radiographic sacroiliitis according to mod. New York criteria

Sensitivity 82.9%, specificity 84.4%; n=649 patients with chronic back pain and age at onset <45 yrs.
Imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and a specificity of 97.3%. ** Note: Elevated CRP is considered a SpA feature in the context of chronic back pain

Rudwaileit, *Ann Rheum Dis* 2009

ASAS criteria 2009

Classification criteria for peripheral spondyloarthritis

Arthritis or Enthesitis or Dactylitis

plus ≥ 1 of:
– Psoriasis
– Inflammatory bowel disease
– Preceding infection
– HLA-B27
– Uveitis
– Sacroiliitis on imaging (radiographs or MRI)

or

plus ≥ 2 of the remaining:
– Arthritis
– Enthesitis
– Dactylitis
– IBP in the past
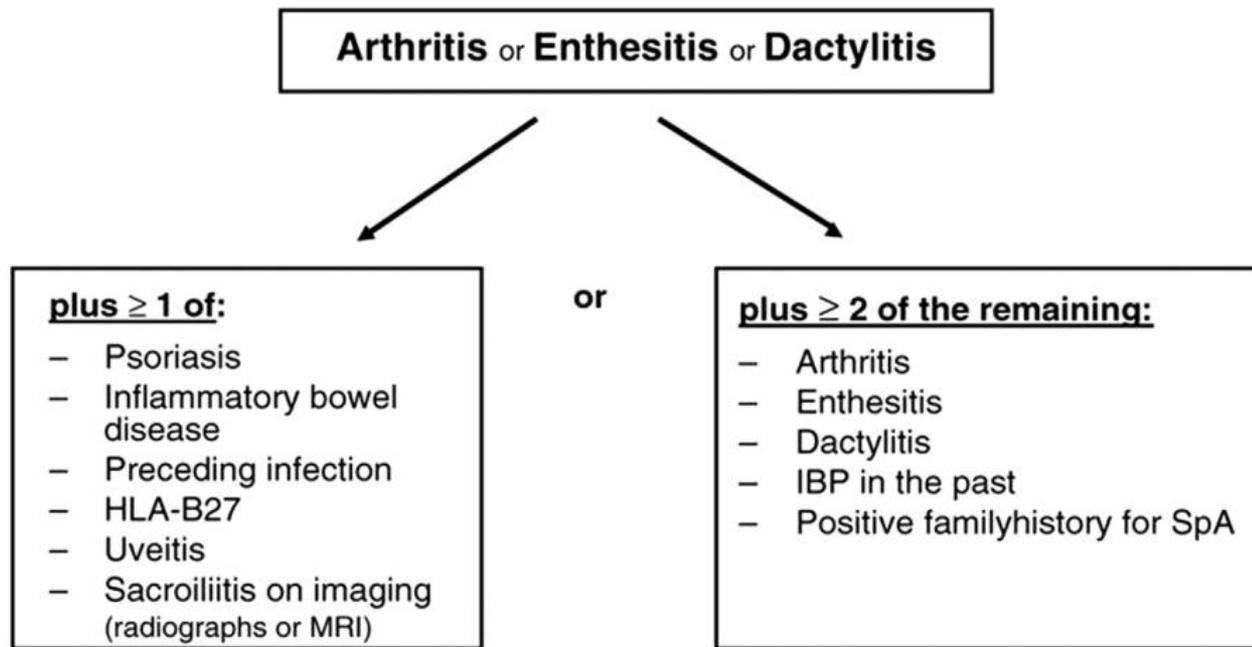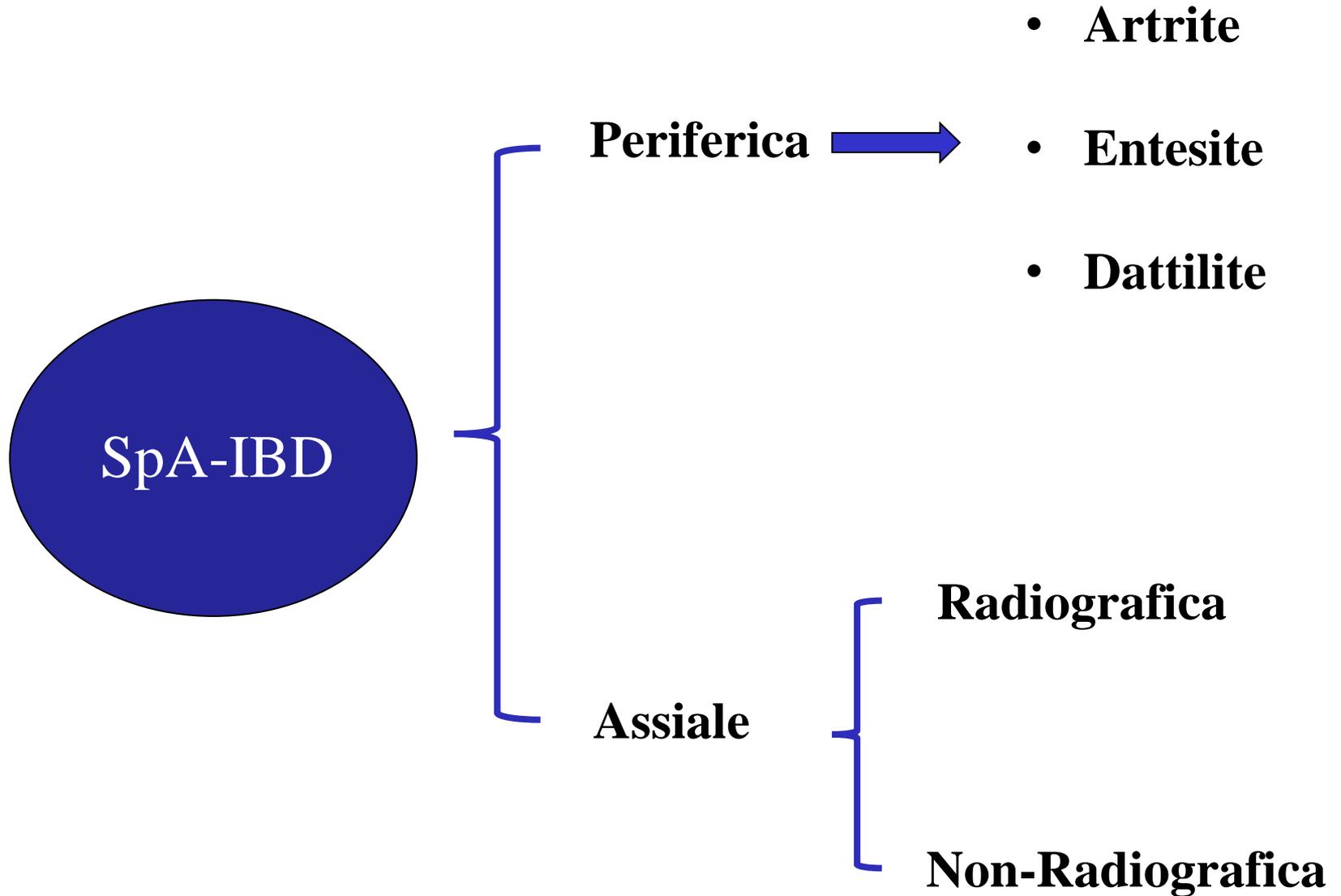– Positive familyhistory for SpA

Fig. 5. Assessment of Spondylo Arthritis International Society (ASAS) classification criteria for axial and peripheral spondyloarthritis. (Adapted from Rudwaleit et al. [37]).

Rudwaileit, *Ann Rheum Dis* 2009

Classificazione dell'artrite periferica

Tipo 1 (pauciarticolare)
< 5 articolazioni: **ginocchio, caviglia, anca**
episodi acuti, self-limiting
coincide con relapse IBD
si associa ad altre manifestazioni (uveiti, PG, EN)

Tipo 2 (poliarticolare)
≥ 5 articolazioni, prevalente a mani e polsi
persistente
non correla con attività IBD
si associa prevalentemente con le uveiti

Red Flags for appropriate referral of suspected SpA & IBD

SpA clinic

Major red flags suggestive of IBD:
- >3 months persistent diarrhoea
- Nocturnal symptoms
- Perianal fistula or abscess
- Rectal bleeding
- Recurrent abdominal pain

Minor red flags suggestive of IBD:
- Anaemia
- Constitutional symptoms including fever and weight loss
- Family history of IBD
- Oral aphthosis

IBD clinic

Major red flags suggestive of SpA:
- Chronic inflammatory low back pain
- Dactylitis (diagnosed by a doctor)
- Heel/knee enthesitis
- Peripheral joint pain and swelling

Minor red flags suggestive of SpA:
- Anterior uveitis
- Chest wall pain
- Family history of SpA
- Skin psoriasis

Prevalenza delle manifestazioni muscolo-scheletriche

- Ampia variabilità nellà letteratura (17 – 39%)

✓ Durata di malattia

✓ Criteri diagnostici SpA (ESSG >>> ASAS)

✓ Tipologia degli studi

✓ Differenze geografiche (prevalenza HLA B27)

OXFORD

Review Article

The Prevalence and Incidence of Axial and Peripheral Spondyloarthritis in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis

Maren C. Karreman,[a,b] Jolanda J. Luime,[a] Johanna M. W. Hazes,[a]
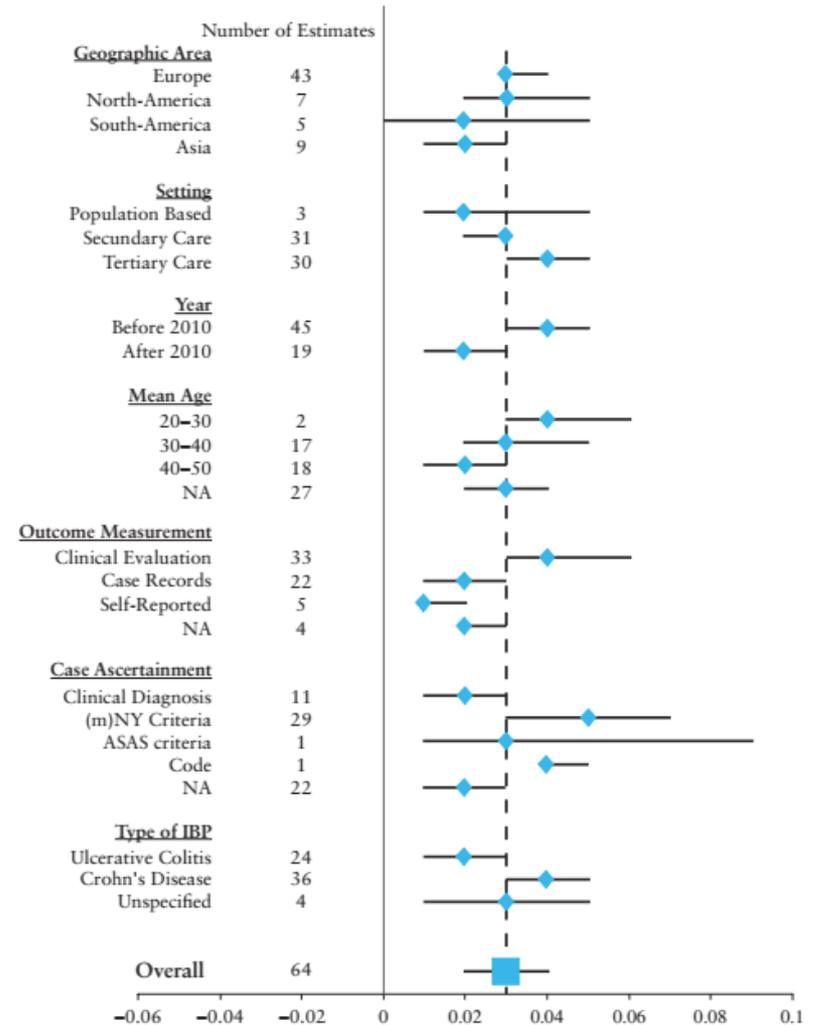Angelique E. A. M. Weel[a,b]

Figure 3. Meta-analysis of the prevalence of ankylosing spondylitis in inflammatory bowel disease [IBD] patients.

OXFORD

Review Article

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Maren C. Karreman,[a,b] Jolanda J. Luime,[a] Johanna M. W. Hazes,[a] Angelique E. A. M. Weel[a,b]

Figure 2. Meta-analysis of the prevalence of sacroiliitis in inflammatory bowel disease [IBD] patients.

OXFORD

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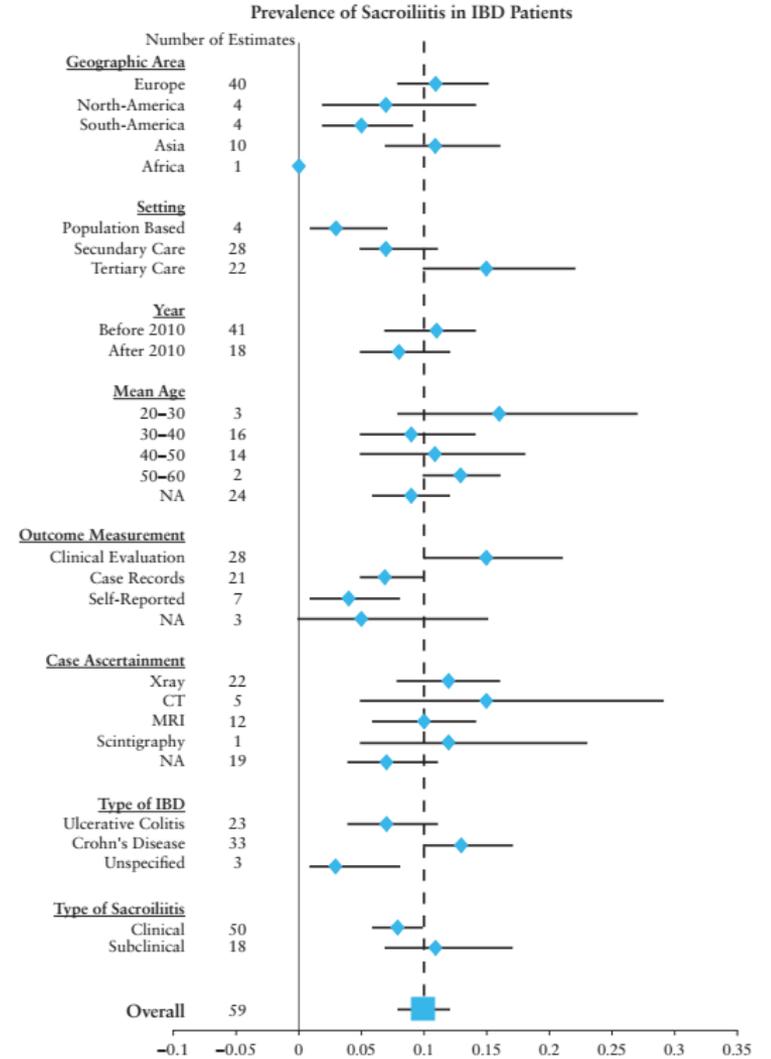Angelique E. A. M. Weel[a,b]

> ➤ Entesite: 1-54%
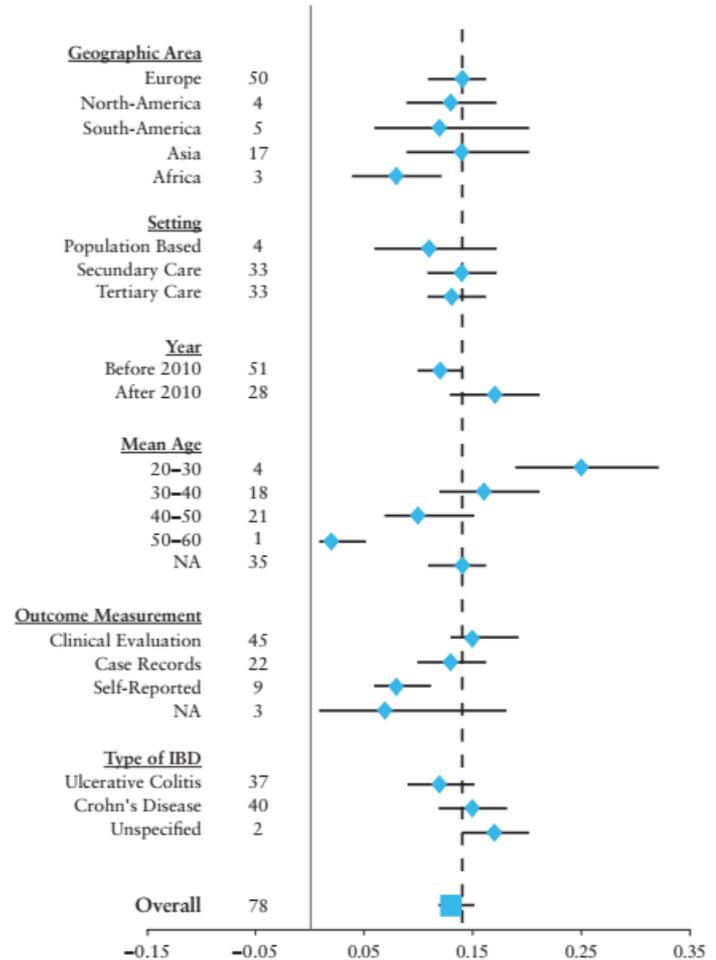>
> ➤ Dattilite: 0-5%

Figure 4. Meta-analysis of peripheral arthritis in inflammatory bowel disease [IBD] patients.
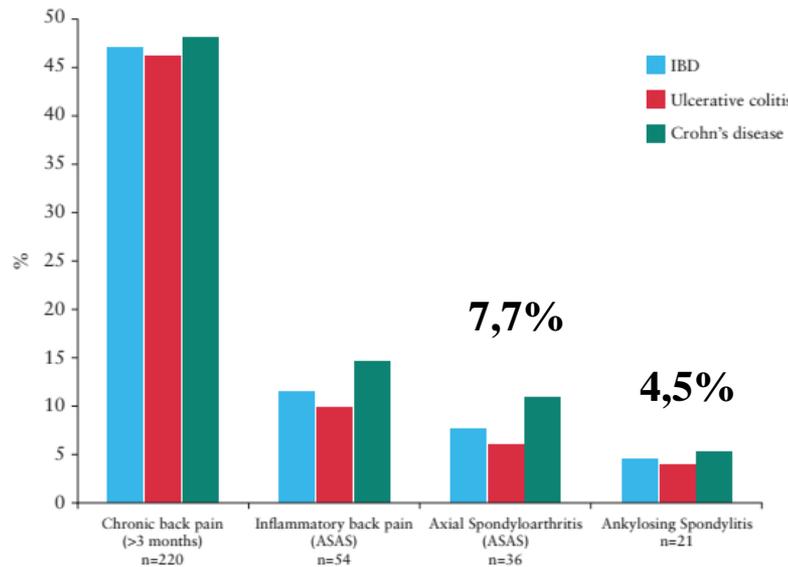
OXFORD

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Original Article

Ankylosing Spondylitis and Axial Spondyloarthritis in Patients With Long-term Inflammatory Bowel Disease: Results From 20 Years of Follow-up in the IBSEN Study

Alvilde M. Ossum,[a,b] Øyvind Palm,[c] Aida Kapic Lunder,[b,d]
Milada Cvancarova,[a,e] Hasan Banitalebi,[d] Anne Negård,[d] Ole Høie,[f]
Magne Henriksen,[g] Bjørn A. Moum,[a,b] Marte Lie Høivik[a]; the IBSEN Study
Group

- **Studio di popolazione**
- **470 pts seguiti per 20 anni**

✓ Prevalenza SA: 3.7 > 4.5%

✓ La maggior parte dei casi entro 5 yrs

✓ 7/8 nuovi casi di SA in RCU

100

A. M. Ossum et al.

7,7% **4,5%**

Legend: IBD, Ulcerative colitis, Crohn's disease

Chronic back pain (>3 months) n=220 · Inflammatory back pain (ASAS) n=54 · Axial Spondyloarthritis (ASAS) n=36 · Ankylosing Spondylitis n=21

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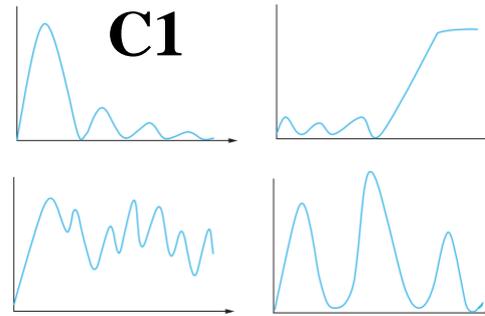
C1

C3/C4
(fenotipo cronico)

Table 3. Disease characteristics for patients with and without back disorders at the 20-year follow-up, n [%].

	Chronic back pain n = 220	Inflammatory back pain [ASAS] n = 54	Axial spondyloarthritis n = 36	Ankylosing spondylitis n = 21	Patients without back complaints n = 242
Females	129 [58.6]*	35 [64.8]*	17 [47.2]	8 [38.1]	102 [42.1]
Age, median [range]	53.7 [27.4–85.2]*	51.1 [36.6–72.2]	50.0 [32.7–85.2]	52.4 [32.6–83.2]	48.8 [28.8–94.0]
UC [n = 314]	145 [46.2]	31 [9.9]	19 [6.1]	13 [4.1]	164 [52.2]
UC extent					
Proctitis/left-sided	76 [52.4]	18 [58.1]	10 [52.6]	6 [46.2]	80 [48.8]
Extensive colitis	69 [47.6]	13 [41.9]	9 [47.4]	7 [53.8]	84 [51.2]
UC onset < 40 years	92 [63.4]	22 [71.0]	13 [68.4]	8 [61.5]	118 [72.0]
CD [n = 156]	75 [48.1]	23 [14.7]	17 [10.9]	8 [5.1]	78 [50.0]
CD onset < 40 years	54 [72.0]*	21 [91.3]	14 [82.4]	7 [87.5]	69 [88.5]
CD location					
Ileal	10 [13.3]	3 [13.0]	2 [11.8]	0	13 [16.7]
Colonic	21 [28.0]	6 [26.1]	3 [17.6]	1 [12.5]	22 [28.2]
Ileocolonic	44 [58.7]	14 [60.9]	12 [70.6]	7 [87.5]	43 [55.1]
CD behaviour					
Non-stricturing, non-penetrating	35 [46.7]*	9 [39.1]	7 [41.2]	5 [62.5]	21 [26.9]
Stricturing/penetrating	40 [53.3]*	14 [60.9]	10 [58.8]	3 [37.5]	57 [73.1]
IBD activity curves [C]					
C1	137 [62.3]	28 [51.9]	16 [44.4]*	10 [47.6]	168 [69.4]
C3/C4	68 [30.9]	20 [37.0]	16 [44.4]*	8 [38.1]	67 [27.7]
Medication ever used					
Corticosteroids	130 [59.1]	37 [68.5]	24 [66.7]	14 [66.7]	139 [57.4]
Biologics	22 [10.0]	9 [16.7]	6 [16.7]	3 [14.3]	23 [9.5]
Immunomodulators	51 [23.2]	16 [29.6]	13 [36.1]	7 [33.3]	61 [25.2]
HLA-B27 positive	30 [13.6]	14 [25.9]*	25 [69.4]*	12 [57.1]*	17 [7.0]
NOD 2	12 [5.5]	2 [3.7]	0	0	13 [5.4]

Prevalence of self-reported spondyloarthritis features in a cohort of patients with inflammatory bowel disease

Carmen Stolwijk MD[1], Marieke Pierik MD PhD[1], Robert Landewé MD PhD[1,2],
Ad Masclee MD PhD[1], Astrid van Tubergen MD PhD[1]

✓ Studio prospettico su 365 pts
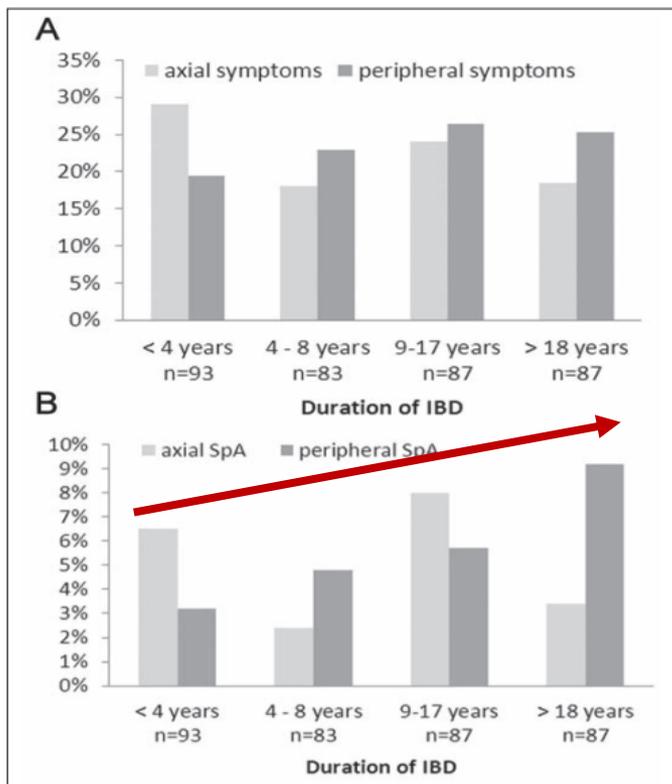
✓ Criteri ASAS

Figure 2) Presence of self-reported spondyloarthritis (SpA) features (A) and diagnosis of either axial or peripheral SpA per quartile of duration of inflammatory bowel disease (IBD) (B)

Manifestazioni muscolo-scheletriche: differenze tra CD e RCU?

Table 3
Clinical details of patients with current articular symptoms.

	UC	CD
Number of patients	28 (7.2%)	34 (12.8%)
Mean age ± S.D. (years)	42 ± 12	40 ± 12
M/F	15/13	18/16
Mean disease duration (years)	9.2 ± 6.7	10.1 ± 6.9
Disease location and extension		
Proctitis	2	
Left sided colitis	9	
Extensive colitis	17	
Ileitis		14
Ileocolitis		10
Colitis		10
Rheumatological diagnosis		
Axial arthropathy:		
Sacroiliitis (%)	8 (2.1)	15 (5.6)
Ankylosing spondylitis (%)	4 (1)	5 (1.9)
Peripheral arthropathy		
Oligoarticular (%)	8 (2.1)	2 (0.7)
Polyarticular (%)	7 (1.8)	7 (2.6)
Fibromyalgia/arthralgia	1 (0.2%)	3 (1.1%)
Tendinitis	1 (0.2%)	1 (0.4%)
Therapy at the time of interview		
Mesalamine	18	13
Sulphasalazine	2	8
Azathioprine	4	4
Steroids	4	12
Other drugs	3	3

- ✓ Maggiore frequenza nel CD con coinvolgimento colico & nella RCU con pancolite

- ✓ Quadro periferico poliarticolare nel CD vs RCU

- ✓ Gender: maschi HLA B27+ > rischio di SA

D' Incà, *Digestive and Liver Dis* 2009

Table 2 Characteristics of peripheral arthropathies in inflammatory bowel disease-related peripheral arthritis

|	UC n: 32 (13.5%)	CD n: 34 (28.3%)	Total IBDPA n: 66 (18.5%)
Age at onset of PA (mean years ± SD)	33.09 ± 10.86 (16–51)	30.63 ± 12.30 (10–68)	31.63 ± 11.70 (10–68)
Median duration of PA (months)	2.92 ± 3.07 (1–12)	4.71 ± 5.05 (1–18)	3.93 ± 4.34 (1–18)
Pre-onset IBD	2 (6.3)	6 (17.6)	8 (12.1)
IBDPA with inflammatory bowel disease activity	19 (59.3)	20 (58.8)	39 (59)
Acute self-limiting episodes	23 (71.8)	17 (50)	40 (60.6)
Recurrent attacks	16 (50)	10 (29.4)	26 (39.3)
Persistent IBDPA symptoms	14 (43.7)	15 (44.1)	29 (45.7)
Symmetrical involvement	12 (38.7)	22 (65.4)	33 (50)
IBDPA in ongoing medical treatment	26 (81.2)	22 (64.7)	48 (72.7)
Arthritic resolution with IBD treatment	20 (62.5)	27 (79.4)	47 (71.2)
Surgery	3 (9.4)	9 (26.5)	12 (18.2)

Surgery: colectomy in UC, resection in CD
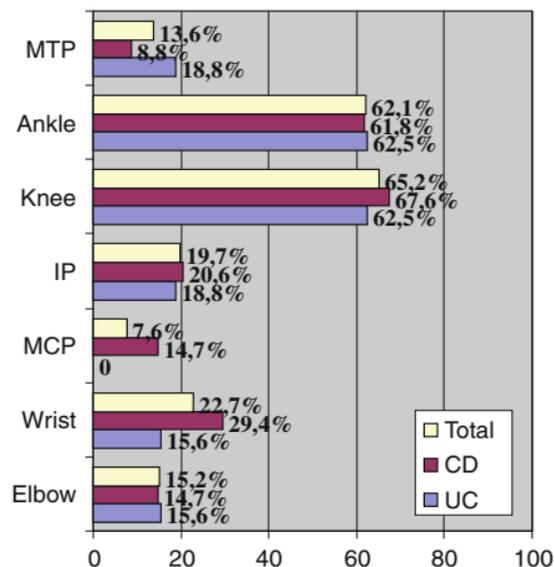
Table 3 Extra-intestinal manifestations of patients with and without IBDPA

	IBDPA + n: 66 (18.5%)	IBDPA − n: 291 (81.5%)
Age at onset of IBD (mean years ± SD)	31.55 ± 10.75 (13–62)	35.32 ± 13.25 (10–72)
Males/females	26 (39.4)/40 (60.6)*	180 (62.9)/111 (38.1)
CD/UC	34 (51.5)/32 (48.5)**	86 (29.6)/205 (70.4)
Erythema nodosum	11 (16.7)***	15 (5.2)
Pyoderma gangrenosum	7 (10.6)****	1 (0.3)
Uveitis	3 (3.5)	3 (1)
Aphthous stomatitis	24 (36.4)	19 (37.5)
Genital ulcer	3 (4.5)	12 (4.1)

Yuksel, *Dig Dis Sci* 2010

Elena Bertolini , Pierluigi Macchioni , Fernando Rizzello ,
Marco Salice , Gentiana Vukatana , Gilda Sandri , Angela Bertani ,
Giovanni Ciancio , Marcello Govoni , Angelo Zelante ,
Nazzarena Malavolta , Marina Beltrami , Carlo Salvarani
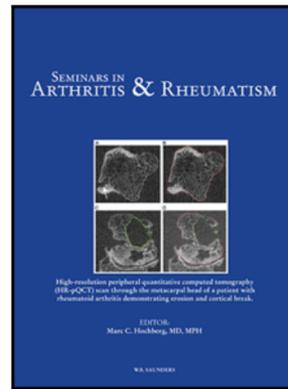
- ✓ Studio multicentrico, cross-sectional su 148 IBD-pts

- ✓ All' esame clinico il 33% dei pts presentavano segni di entesite attiva (vs artrite riscontrata nel 19.6%)

- ✓ Maggiore prevalenza nella RCU

- ✓ Al doppler prevalenza di alterazioni enteseali nell' 87.8% dei pts

# Esiste una flogosi (MSK) subclinica nei pazienti IBD?

TABLE 2 | Distribution of ultrasound findings in IBD patients and control population (IBS and HC).

	Enthesophyte	Structure	Thickness	Burs
IBD with SpA	7 (0–13)	9 (3–14)	6 (0–9)	1.5 (
IBD without SpA	6 (2–14)	6 (0–13)**	4 (0–8)	2 (0
IBS	3 (0–12)*	0 (0–9)*	1 (0–12)*	0 (0
HC	4 (0–12)*	1.5 (0–7)*	1.8 (1.9)*	1 (0
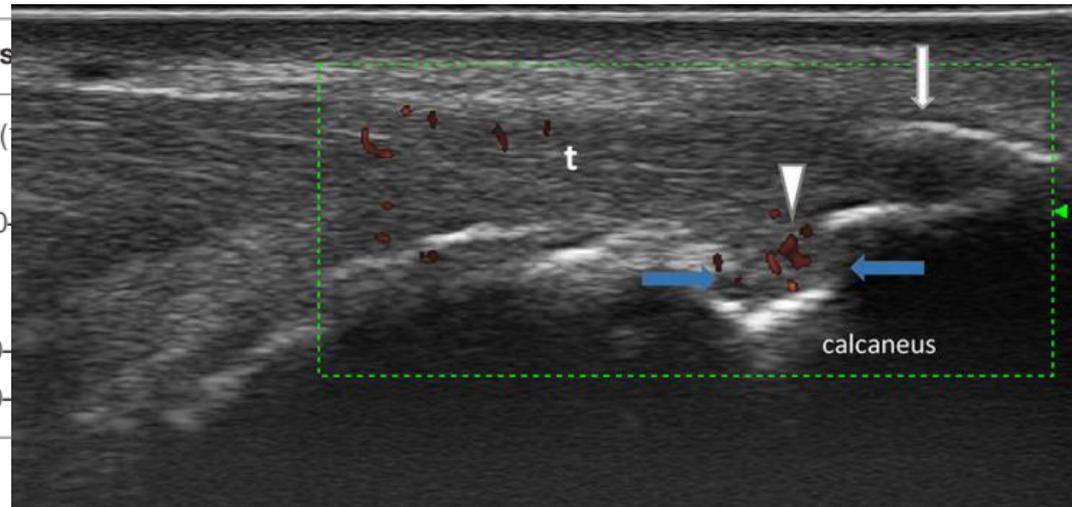
✓ L' entesite subclinica è estremamente comune nei pz IBD (**67%** almeno 1 segnale PD)

✓ Segni ecografici di entesite attiva (PD+) sono egualmente presenti nei pz IBD, indipendentemente dalla clinica

✓ La presenza di **erosioni** correla con la diagnosi di SpA-IBD
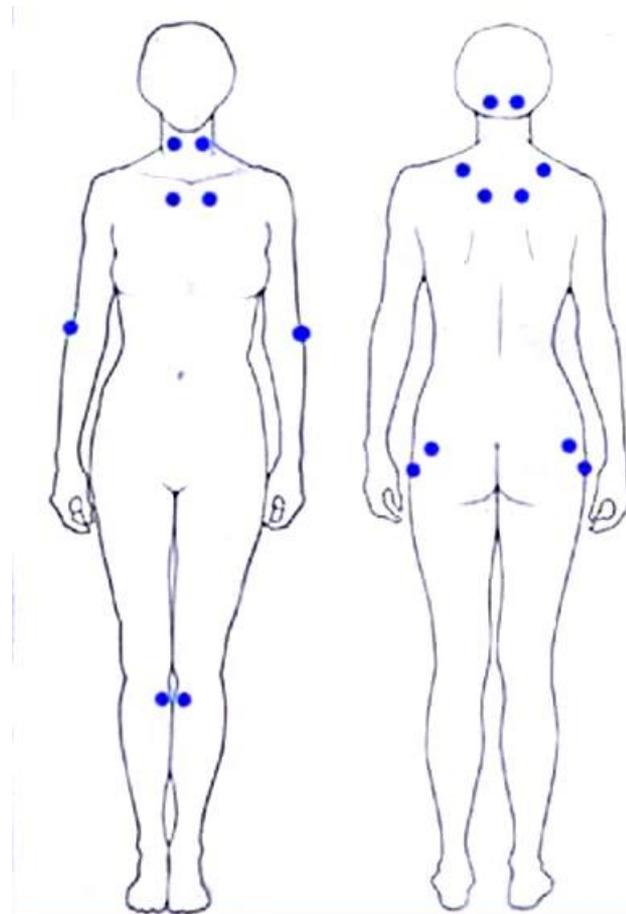
IBD: polientesite o fibromialgia?
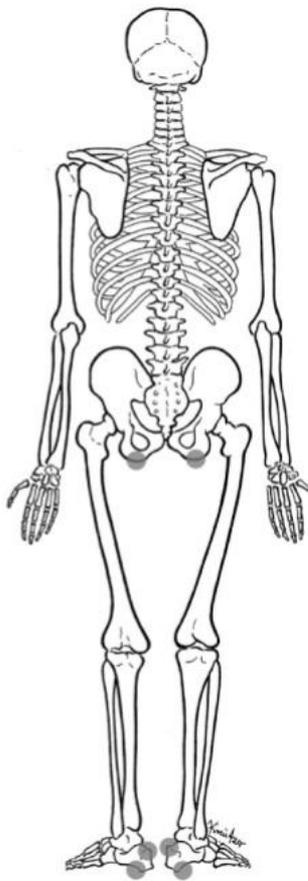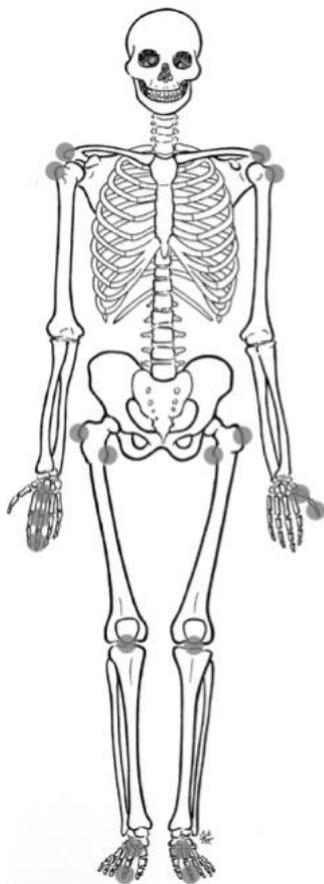
Figure 1 Most commonly affected appendicular entheseal sites in spondyloarthritis.

RHEUMATOLOGY

Original article

Clinical and sonographic discrimination between fibromyalgia and spondyloarthopathy in inflammatory bowel disease with musculoskeletal pain

Federica Martinis[1,*], Ilaria Tinazzi[2,*], Elena Bertolini[3], Giorgia Citriniti[4], Angela Variola[5], Andrea Geccherle[5], Antonio Marchetta[2], Dennis McGonagle[6] and Pierluigi Macchioni[4,7]

✓ Studio clinico – ecografico su **301 IBD-pts**

✓ Valutazione SFM in base a 2010 ACR criteria

✓ SpA diagnosi: ASAS criteria

12,3%

	IBD (264 pts)	IBD + FM (37 pts)	P
Male/female (%)	133/131 (49/51)	7/30 (19/81)	<0.001
Age, mean (S.D.)	42.8 (14)	50.3 (12.4)	0.002
BMI, mean (S.D.)	23.8 (4.9)	23.5 (5.8)	n.s.
IBD subtype, n (%)			0.025
CD	125 (48)	25 (67)	
UC	136 (52)	12 (32)	
Partial Mayo Score (77 patients), n (%)			n.s.
0	22 (54)	3 (75)	
1	12 (29)	0	
2	5 (12)	1 (25)	
3	2 (5)	0	
HBI class (68 patients), n (%)			n.s.
0	32 (68)	1 (100)	
1	9 (19)	0	
2	4 (9)	0	
3	2 (4)	0	
IBD duration, months (S.D.)	116 (117)	154 (148)	n.s.
Ongoing therapy with biologic drugs, n (%)	78 (30)	13 (35)	n.s.
Psoriasis, n (%)	15 (8.8)	2 (7.4)	n.s.
Smoking, n (%)	27 (16.8)	4 (16)	n.s.

Martinis, *Rheumatology* 2020

	IBD (98) (A)	IBD + FM (13) (B)	IBD + SpA (46) (C)	P (A vs B)	P (A vs C)	P (B vs C)
Enthesis acute changes, mean (s.d.)	0.6 (1.2)	0.7 (0.5)	1.7 (2.1)	n.s.	n.s.	0.009
Patient with >1 enthesis with acute changes, n (%)	30 (31)	7 (54)	28 (62)	n.s.	n.s.	n.s.
Entesis with chronic changes, mean (s.d.)	3.8 (2.6)	3.2 (2.3)	3.4 (2.8)	n.s.	n.s.	n.s.
Patients with >1 enthesis with chronic changes, n (%)	81 (83)	12 (92)	38 (84)	n.s.	n.s.	n.s.
Enthesis power Doppler positive, mean (s.d.)	0.3 (1.0)	0.5 (1.4)	1.3 (1.5)	n.s.	<0.001	<0.001
Patients with >1 enthesis power Doppler positive, n (%)	14 (14)	3 (23)	26 (58)	n.s.	<0.001	0.028
Enthesis alteration >1, n (%)	75 (87)	14 (93)	44 (90)	n.s.	n.s.	n.s.
GUESS, mean (s.d.)	6.1 (3.7)	4.5 (2.9)	6.1 (4.1)	n.s.	n.s.	n.s.
MASEI, mean (s.d.)	9.5 (7.8)	7.2 (7.4)	11.2 (8.5)	n.s.	n.s.	<0.001

✓ Quasi la totalità dei pts (94.5%) presentavano almeno un segno ecografico di entesopatia

✓ Nei pts con SpA-IBD prevale la positività del segnale power doppler ed il carico lesionale globale

Martinis, *Rheumatology* 2020

Fig. 1 Thickness of rotuleus tendon [proximal (PRT) and distal (DRT) entheses] (**A**, **B**); thickness and enthesophytosis of plantar fascia (PF) (**C**). Mild (**D**), moderate (**E**) and severe (**F**) PD signal in Achilles tendon entheses (AT).
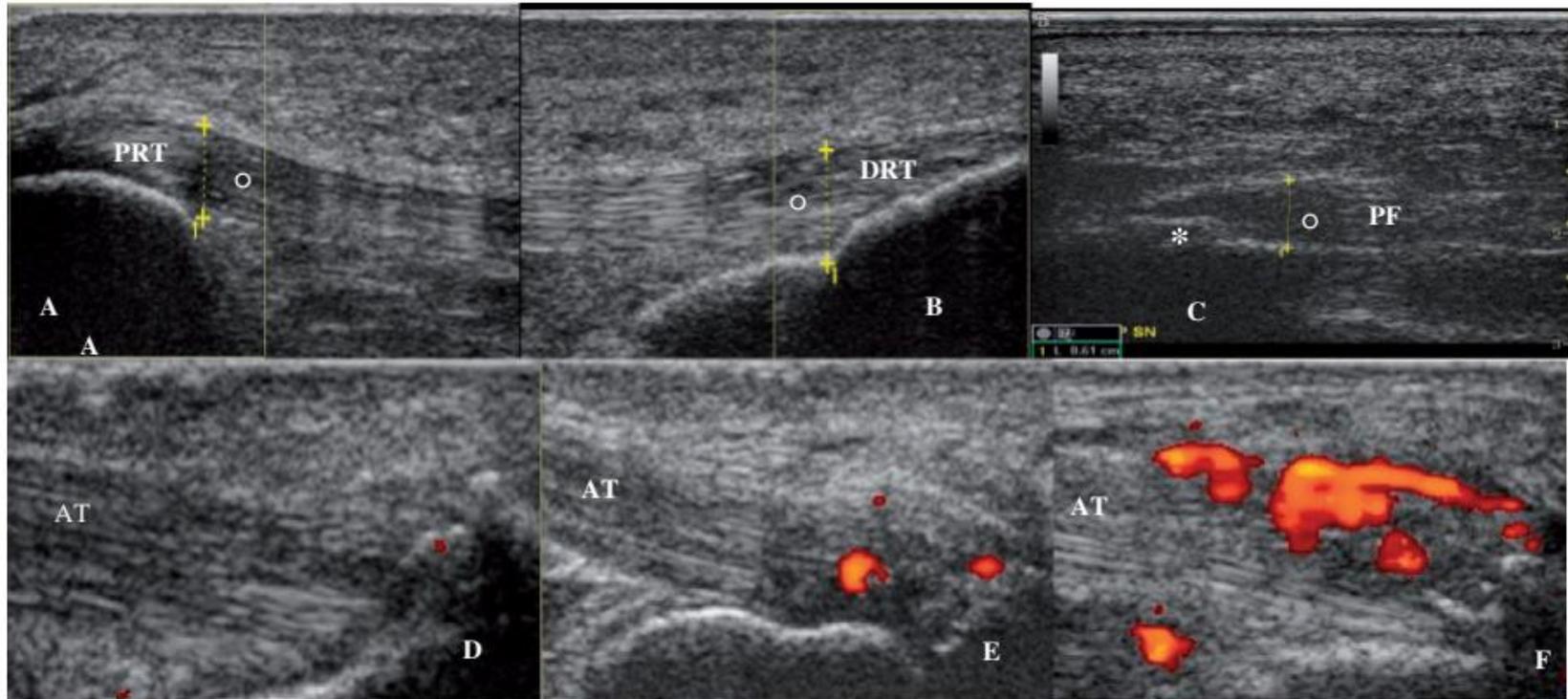
✓ L' ecografia ha un ruolo essenziale nella diagnosi di entesite

✓ I reperti ecografici vanno sempre interpretati e correlati con il quadro clinico

RMD Open
Rheumatic & Musculoskeletal Diseases

Impact of biological therapy in reducing the risk of arthritis development in inflammatory bowel diseases

Mauro Fatica,[1] Benedetta Monosi,[1] Paola Conigliaro [ID] ,[1] Arianna D'Antonio,[1]
Sara Essofi,[2] Elisa Cuccagna,[2] Alberto Bergamini,[1] Livia Biancone,[2]
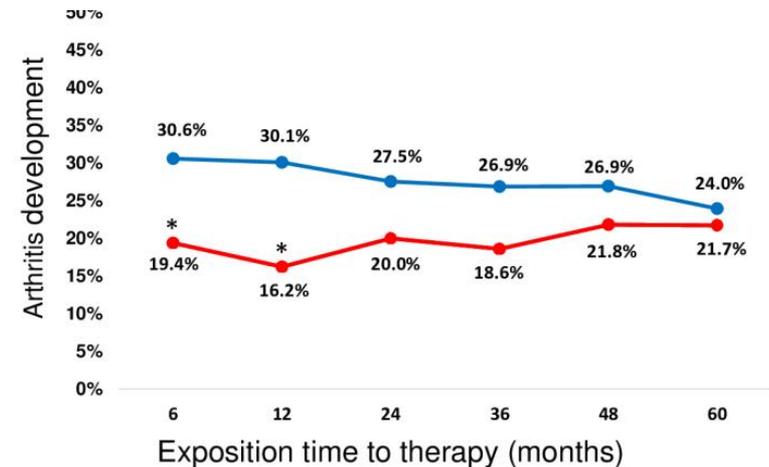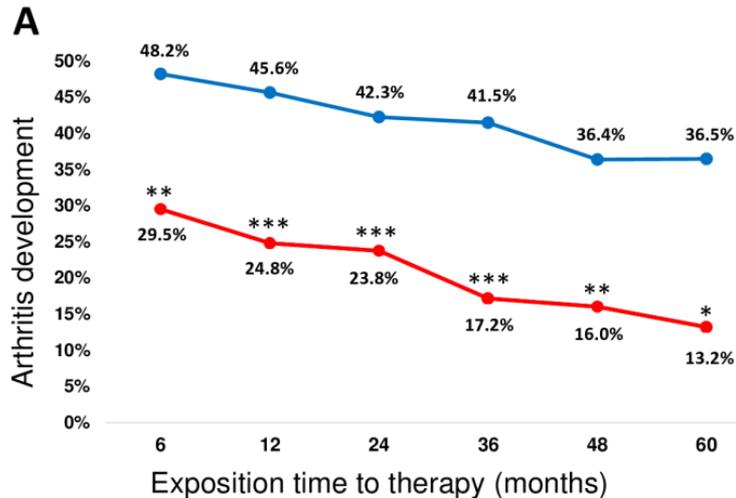Giovanni Monteleone,[2] Paola Triggianese,[1] Emma Calabrese,[2]
Maria Sole Chimenti [ID] [1]

✓ Analisi retrospettiva di coorte monocentrica

✓ Periodo di osservazione di 10 anni

✓ 507 IBD pts (288 CD, 219 RCU)

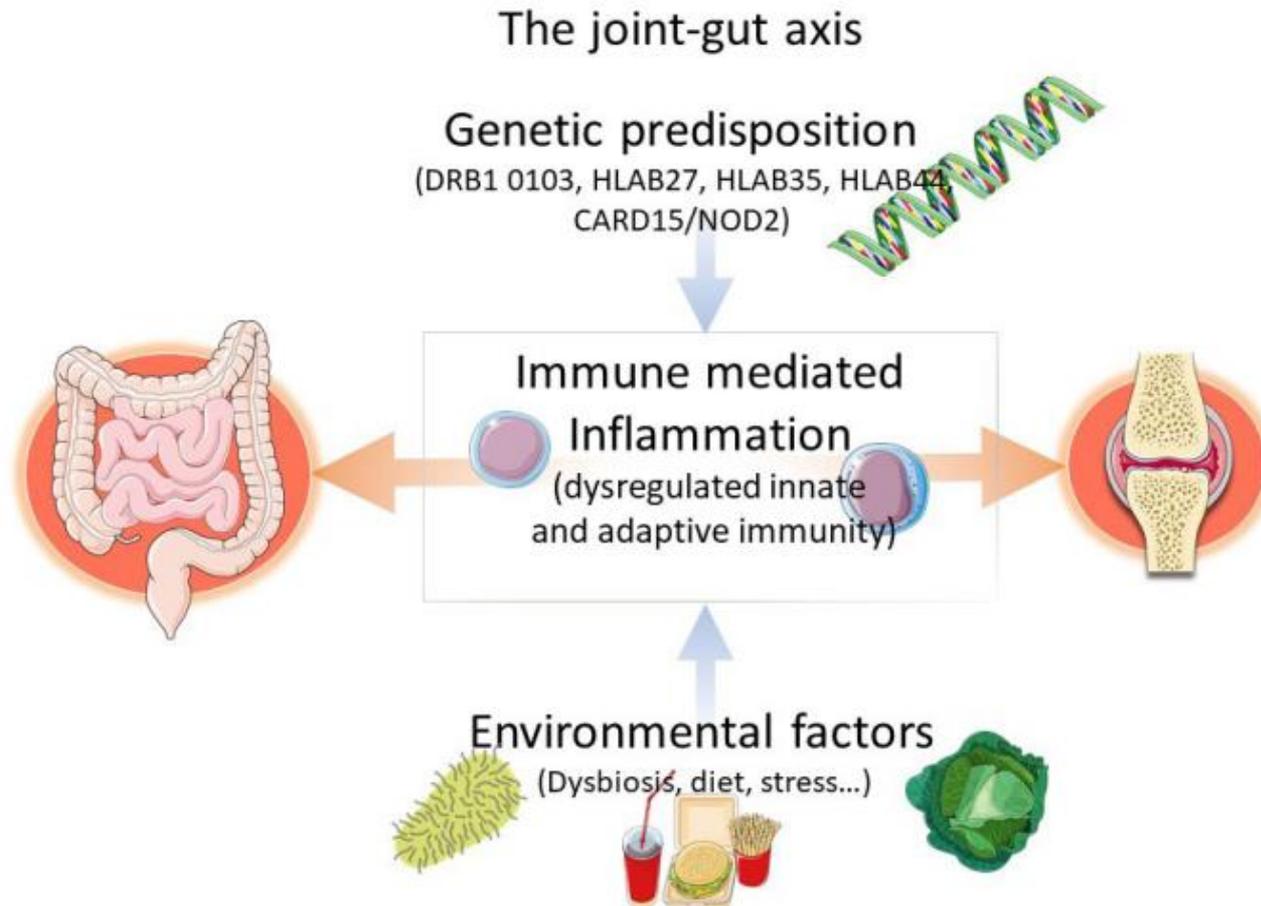✓ SpA diagnosi: ASAS criteria

SpA-CD: 106/288

SpA-RCU: 56/219
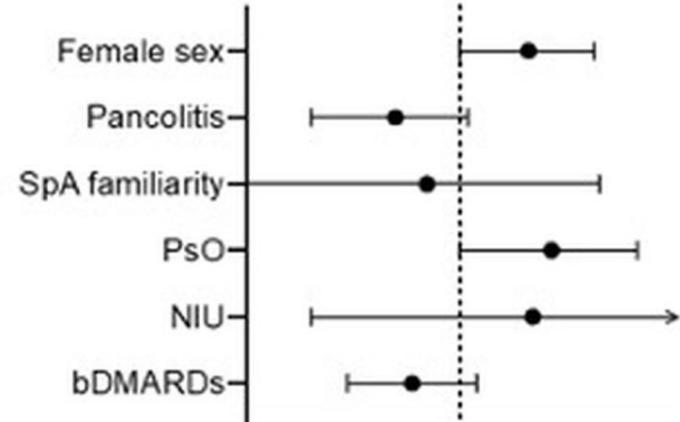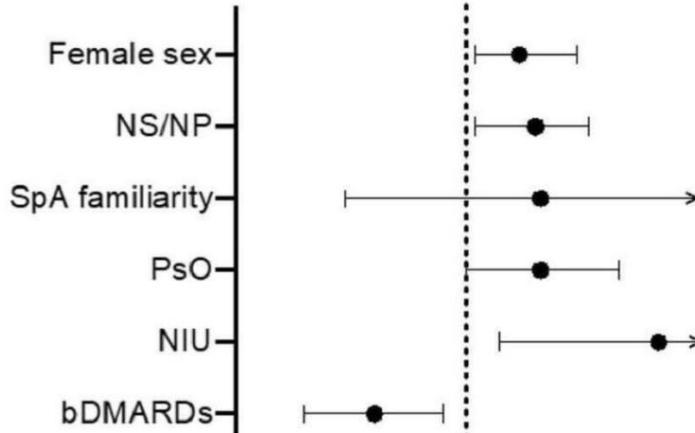
Conclusions bDMARDs treatment had an impact in reducing SpA development and clinical associated risk factors to transition from IBD to IBD-SpA emerged.

Fisiopatologia
«gut-synovial axis» hypothesis

The joint-gut axis

Genetic predisposition
(DRB1 0103, HLAB27, HLAB35, HLAB44,
CARD15/NOD2)

Immune mediated Inflammation
(dysregulated innate and adaptive immunity)

Environmental factors
(Dysbiosis, diet, stress...)

Fauny et al., *Ann Rheum Dis* 2020

Patogenesi

Guselkumab
Tildrakizumab
Risankizumab

Secukinumab
Ixekizumab
Netakimab

Bimekizumab

Brodalumab

IL-23 p19 p40 → **Th17** → IL-17A/A — IL-17F/F — IL-17A/F → IL-17RA IL-17RC

Ustekinumab

ABT122

IL-12 p35 p40 → **Th1** → TNF-α → Inflammation

Tsukazaki, *Int J Mol Sci* 2020

Terapia: a "patient-tailored" approach

✓ Il trattamento deve tenere conto del tipo di coinvolgimento articolare, del tipo di IBD in termini di attività/estensione di malattia, della presenza di manifestazioni extra-intestinali e delle comorbidità

✓ Assenza di significativi dati *evidence-based*

✓ Terapia *condivisa* reumatologo-gastroenterologo

REVIEW ARTICLE

Update on therapeutic management of spondyloarthritis associated with inflammatory bowel disease

Dorra Ben Nessib [1,2,3] ⓘ · Hanene Ferjani [1,2,3] · Kaouther Maatallah [1,2,3] · Safa Rahmouni [1,2,3] · Dhia Kaffel [1,2,3] · Wafa Hamdi [1,2,3]

Table 1 | Conventional systemic treatments for SpA and IBD

Drug	Peripheral SpA	Axial SpA	Crohn's disease	Ulcerative colitis
NSAIDs	Recommended according to international guidelines[261]	Approved by the FDA and/or EMA	Avoid in active disease	Avoid in active disease
Systemic glucocorticoids	Approved by the FDA and/or EMA	Not effective[262]	Approved by the FDA and/or EMA (ineffective at maintaining remission[263])	Approved by the FDA and/or EMA
Sulfasalazine	Recommended according to international guidelines[261]	Recommended according to international guidelines[152]	Approved by the FDA and/or EMA (only modestly effective[264])	Approved by the FDA and/or EMA
Methotrexate	Approved by the FDA and/or EMA	Not effective[265,266]	Approved by the FDA and/or EMA	Not effective[267]
Leflunomide	Approved by the FDA and/or EMA	Not effective[268]	Not evaluated in RCT[269]	Not evaluated
Azathioprine	Not evaluated	Not evaluated	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA

IBD, inflammatory bowel disease; RCT, randomized controlled trial; SpA, spondyloarthritis.

Table 2 | Approved biologic and small-molecule drugs for SpA–IBD

Target	Drug class	Therapeutics	Approval status			
			Peripheral SpA	Axial SpA	Crohn's disease	Ulcerative colitis
TNF	mAb	Adalimumab; infliximab; certolizumab; golimumab	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA (only adalimumab, infliximab and certolizumab)	Approved by the FDA and/or EMA (only adalimumab, infliximab and golimumab)
p40 subunit (IL-12/IL-23)	mAb	Ustekinumab	Approved by the FDA and/or EMA	Not effective	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA
p19 subunit (IL-23)	mAb	Risankizumab	Approved by the FDA and/or EMA	Not effective	Approved by the FDA and/or EMA	Ongoing phase III clinical trial
JAK1 and JAK3	Small molecule	Tofacitinib	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA	Not effective	Approved by the FDA and/or EMA
JAK1	Small molecule	Upadacitinib	Approved by the FDA and/or EMA	Approved by the FDA and/or EMA	Phase III clinical trial with positive results	Approved by the FDA and/or EMA

IBD, inflammatory bowel disease; JAK, Janus kinase; mAb, monoclonal antibody; SpA, spondyloarthritis.

Cozzi, *Nat Rev Rheumatol* 2023

Conclusioni

- Le manifestazioni muscolo-scheletriche rappresentano le più comuni complicanze extra-intestinali nelle IBD

- Una stretta collaborazione tra specialisti nel contesto di un team multidisciplinare è cruciale per la diagnosi precoce delle complicanze, per la scelta della terapia più idonea e per il raggiungimento degli outcome