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Fatouma SALEM[1], Nadège KINDT[1], Julian R MARCHESI[2,3], Patrick NETTER[1], Anthony LOPEZ[4,5], Tunay KOKTEN[4], Silvio DANESE[6], Jean-Yves JOUZEAU[1], Laurent PEYRIN-BIROULET[4,5]* and David MOULIN[1,7]*

[1] IMoPA, UMR7365 CNRS-Université de Lorraine, Vandœuvre Les Nancy, France

[2] Division of Integrative Systems Medicine and Digestive Disease, Imperial College London, England

[3] School of Biosciences, Museum Avenue, Cardiff University, Cardiff, UK

[4] NGERE, UMR_ U1256 INSERM-Université de Lorraine, Vandœuvre Les Nancy, France

[5] Service d'hépato-gastroentérologie, CHRU de Nancy, Vandœuvre Les Nancy, France

[6] Department of Biomedical Sciences, Humanitas University, Rozzano, Milan , Italy.

[7] CHRU de Nancy, Contrat d'interface, Vandœuvre Les Nancy, France

*Authors contributed equally to this work and are corresponding:

Laurent PEYRIN-BIROULET: peyrinbiroulet@gmail.com, Service d'hépato-gastroentérologie, CHRU de Nancy, Vandœuvre Les Nancy, France

David MOULIN: david.moulin@univ-lorraine.fr; IMoPA, UMR7365 CNRS-Université de Lorraine, Vandœuvre Les Nancy, France

Contributors
FS and NK: study concept and design;acquisition, analysis, review and interpretation of data;manuscript preparation and critical revisions. NK: study concept and design; review and interpretation of data;manuscript preparation and critical revision. JRM, PN, AL, TK, SD: review and interpretation of data;manuscript preparation and critical revisions. JYJ, LPB DM: study concept and design; review and interpretation of data; manuscript preparation and critical revisions; study supervision.

Competing interests
The authors declare to have no conflict of interest.

ABSTRACT

Introduction: Inflammatory bowel diseases (IBD), and Chronic Rheumatic Diseases (CRD) are systemic chronic disorders sharing common genetic, immune and environmental factors. About half of patients with IBD develop rheumatism affections and microscopic intestinal inflammation is present in up to half of CRD patients. IBD and CRD patients also share a common therapeutic armamentarium. Disequilibrium in the complex realm of microbes (known as dysbiosis) that closely interact with the gut mucosal immune system, has been associated with both IBD and CRD (Spondyloarthritis and Rheumatoid Arthritis). Whether dysbiosis represents an epiphenomenon or a prodromal feature remains to be determined.

Methods: In an attempt to further interrogate whether specific gut dysbiosis may be the missing link between IBD and CRD in patients developing both diseases, we performed here a systematic literature review focusing on studies looking at bacterial microbiota in CRD and/or IBD patients.

Results: We included 80 studies, with a total of 3799 IBD patients without arthritis, 1084 CRD patients without IBD, 132 IBD patients with arthropathy manifestations and 12 SpA patients with IBD history. Overall, this systematic review indicates that an increase in *Bifidobacterium, Staphylococcu*s, *Enterococcus, Lactobacillus, Pseudomonas, Klebsiella* and *Proteus* genera, as well as a decrease in *Faecalibacterium, Roseburia* genera and species belonging to Verrucomicrobia, Fusobacteria phyla are common features in IBD and CRD patients, whereas dozens of bacterial species are specific features of CRD and IBD.

Conclusion: Further work is needed to understand the functions of bacteria and of their metabolites but also to characterize fungi and viruses that are commonly found in these patients.

Introduction

Inflammatory bowel diseases (IBD), are mainly represented by Crohn's disease (CD) and ulcerative colitis (UC), whereas Chronic Rheumatic Diseases (CRD), encompass Rheumatoid Arthritis and Spondyloarthritis (SpA). These systemic chronic disorders have relapsing and remitting clinical course arising from an interaction between genetic, immune and environmental factors.

CRD and IBD are intercurrent since articular manifestations are observed in up to 40% of IBD patients and intestinal inflammation is often present in CRD subjects [1]. Co-occurring CRD and IBD can be very disabling and are associated with a more severe disease course in IBD patients[2].

Interestingly, IBD and CRD share common pathophysiology, including common molecular and cellular actors and, consequently, common therapeutic armamentarium. Genetic studies have reinforced the importance of genes and pathways contributing to IBD pathogenesis, such as barrier function, the role of T cell subsets, and cytokine-cytokine receptor signalling [3]. In addition, recent studies pointed out new genes and pathways, including autophagy or regulation of interleukin 23 (IL23) signalling, highlighting the importance of host defence pathways, specifically those involved in the management of mycobacteria [4]. Heredity is also an important feature of CRD and notably in SpA, and several genetic polymorphisms have been shown to influence the disease risk. The most important one is the major histocompatibility complex (MHC) class I allele HLA-B27 [5]. Remarkably, a large subset of the IBD and CRD susceptibility identified genes are encoding for proteins involved in immune response, and particularly in the IL-23/Th17 pathway of T cell differentiation, which is primarily implicated in response against extracellular pathogens, including bacteria and yeasts, and/or in microbial sensing.

However, the link between pathological gut and joint inflammation in patients with both IBD and CRD is not fully understood. Taken together, these data suggest that the perturbation of the gut microbiome, also called dysbiosis represent an attractive target in this context.

In an attempt to further interrogate whether specific gut dysbiosis may be associated with IBD and CRD and promote pathological inflammation within joint-gut axis, we performed a systematic literature review investigating similarities and differences regarding faecal microbiota in these patients.

Methods

Search strategy and study selection

A systematic literature search was performed according to PRISMA guidelines [6]. The literature review conducted using PubMed/MEDLINE (from 1950 to December 2018), Web of science (from 1958 to December 2018). Abstracts from annual meetings of national and international gastroenterology and rheumatology conferences (United European Gastroenterology Week [UegW], Digestive Diseases Week [DDW], European Crohn's and Colitis Organization [ECCO], European League Against Rheumatism [EULAR], American College of Rheumatology [ACR]) were searched manually from 2013 to 2018.

The following keywords were searched in various combinations using the boolean terms “AND” and “OR” ("Microbiota", "Microbiome", "Gut", "Gastrointestinal Microbiome","Microbiology", "Colitis", "Ileitis", "Intestinal", Enteritis", "Inflammatory Bowel Diseases", "Crohn Disease", "Ulcerative Colitis" , “Rheumatoid Arthritis”, "Spondyloarthritis" ,"Arthritis", "Reactive Arthritis", "Psoriatic Arthritis", "Rheumatoid Arthritis", "Infectious Arthritis", "Ankylosing Spondylitis", " Mycobiome", "Fungal Microbiota", "Intestinal Virome"). This strategy was used both as Medical Subject Headings (MeSH) terms if available and as free text. Searching was limited to publications with human subjects. We only selected English language full text papers and abstracts.

Two authors independently reviewed all articles. Inclusion criteria included the presence of IBD and CRD patient samples and 16S rRNA gene sequencing or metagenomic methods to characterize the gut microbiota. Literature reviews did not include meta-analyses, as well as experimental studies based on *in vitro* findings and animal models.

Study characteristics and outcomes were reported in a Microsoft Excel Office 2016 Professional spread sheets.

Results

6519 were identified (Fig 1) based on defined criteria. After review of the titles and abstracts 5564 papers were excluded. Amongst the remaining studies, another 881 were excluded because they included reviews, data retrieved from studies using animal models and *in vitro* findings. Therefore, 80 studies were included: 56 from IBD patients, with 1 Case-reports [39] (Table 1.a, 1.b and 1.c), 21 from CRD patients (RA and SpA) including 5 congress abstracts [78,80,81,84,85] (Table 2.a and 2.b). Finally, three publications addressed gut microbiota study in IBD patients developing arthropathy [94,96,97] (Table 3). As microbiota from one individual is different from one sample location to another, table were generated by sample type and are detailled with studied populations characteristics.

1. Literature search results

A. Distinct dysbiosis in IBD and CRD

In order to identify bacterial variations specific of IBD, (i.e. not found in CRD), and vice versa, we adopted two complementary methodologies: we first reviewed bacterial changes reported in studies enrolling IBD patients without information on possible concomitant arthritis, then all studies involving CRD patients without information on possible concomitant IBD. We looked finally at studies comparing gut microbiome in patients with or without IBD-associated CRD.

A.1. Gut bacterial changes reported in IBD patients

Fifty-six studies enrolling 3270 IBD patients from which gut microbiota was mainly analyzed by 16S rRNA gene sequencing or qRNA of DNA extracted from faeces and/or biopsies. A quantitative and qualitative (biodiversity) reduction of the gut microbiome in IBD patients [7,8] is generally observed.

Firmicutes phyla

A reduction of *Clostridiales* order species from the Firmicutes phylum is observed in the faecal microbiota of IBD and CD patients [9–11].Whereas an enrichment of *R.gnavus* is observed in the IBD patients faecal microbiota [12–14]. This phylogenetic group includes several butyrate-producing bacteria, notably *Faecalibacterium and Ruminococcus*, which are among the main members of the *Ruminococcaceae* genera [15]. Other bacteria that are considered as 'beneficial' for the host have been shown to be quantitatively reduced in the faecal microbiota of these patients. A few studies found a lower number of sequences of the bacterial phylum Firmicutes in the mucosal-associated microbiota (MAM) of CD and UC patients, especially species from the *Lachnospiraceae* genera (*Roseburia* and *coprococcus*) [12,13,16,17, ,18,19,20,21]. Within this phylum, an increase amount of *Streptococcus* genera was observed, in contrast to *Ruminococcaceae* genera (*Faecalibacterium*) that seems to be particularly deficient in CD [15,20,22–24]. Furthermore, Rehman *et al* demonstrated a population-specific disease-related patterns of Firmicutes phyla, by observing a lower abundance in healthy German samples compared with patients samples, while Lithuanian and Indian patients with CD show the lowest Firmicutes abundances [25].

In a recent study using molecular methods of bacterial identification [19], it has been shown that *F. prausnitzii* was one of the most underrepresented species of the *Faecalibacterium* genera in the MAM of patients with IBD (compared with healthy subjects) [12,13,15,19,22,23,26–29]. Therefore, similar to the results from faecal microbiota studies, a significant decrease of bacteria from the Firmicutes phylum was demonstrated in the MAM of CD patients [15,22,23].

A reduction of *Ruminococcaceae, Lactobacillaceae, Veillonellaceae* and *Erysipelotrichiaceae* genera (*Faecalibacterium, Streptococcus, Veillonella* and *Catenibacterium* respectively*)* [10,13,30–32], along with *Dialister* genus in CD patients[33], and *Roseburia, Clostridium* and

Butyricimonas genus is observed in IBD patients particularly those with UC [15,21,31,32,34] . A few studies, showed an increased amount of the *Tissierellaceae* family, and a decreased number of *Eubacterium* genera in inflamed colonic mucosa biopsy samples when compared to the non-inflamed sites in UC patients [35–37]. (Fig 2)

Bacteroidetes phyla

Data concerning the Bacteroidetes phylum are more conflicting. Some studies reported a reduction of the *Bacteroides* group in IBD patients especially in CD patients [9,12,13,20]. In contrast, Andoh and colleagues demonstrated an increase amount of this phyla in the context of IBD [38]. To note, one study showed an increase of Bacteroidetes phylum in salivary microbiota in UC patients [39]. Hirano and co-workers showed an enrichment of the *Cloacibacterium* genus, and decreased abundance of *Prevotella* (at both inflamed and non-inflamed mucosal site) and *Butyricimonas* genera at the non-inflamed mucosal site of UC patients compared to the corresponding site in non-IBD controls and in the faecal microbiota of UC patients[12,34,35,40]. A greater abundance in these two genera was found in the submucosal tissues of patients with CD [12,34,35,40,41]. As with CD, this strongly suggest a restricted biodiversity in UC and an increased proportion of unusual bacteria [42,43]. Bacteroidetes show also interesting age-related patterns and population-independent increase in abundance in the standing and active bacteria among healthy subjects and UC patients[25].A decrease abundance of *Parabacteroides* genera and *Odoribacteracae* family in IBD and CD patients respectively is reported [10,13,15]. Similar to the results from faecal microbiota studies, a significant decrease of bacteria from the phylum Firmicutes was demonstrated in the MAM of patients with CD [44,45]. A recent study of Walujkar and collagues revealed significant differences in the MAM of patients manifesting acute exacerbations of UC with increased amount of *Parabacteroides* and *Elizabethkingia* genera in the MAM of UC patients as compared to the same patients during remission stage [46] (Fig 2).

Actinobacteria phyla

Concerning the Actinobacteria phylum, studies using both culture and recent molecular methods, demonstrated an increase of *Bifidobacterium* genera in the faecal microbiota as well as in the biopsy samples of IBD patients, notably in patients with CD [12,13,15,19,47]. However, other authors reported an age-related reduction of bacteria of the *Bifidobacterium* genera was

shown in inflamed sites when compared to non-inflamed ones and salivary microbiota of UC patients [12,13,15,47–49,31,35,39,50]. Walujkar and co-workers showed an increase amount of *Micrococcus* genera in MAM of UC patients when compared to non-IBD subjects [46] (Fig 2).

Proteobacteria phyla

Published studies display a quantitative alteration of Proteobacteria phylum in IBD especially *Escherichia* and *Shigella* from the *Enterobacteriaceae* family, [10,12,13,15,24,29,51]. Thus, their increased abundance was reported in the MAM and faecal samples of patients with CD, whether using culture[24,44] or molecular [52,17,53] methods. As with CD patients, the MAM of patients with UC contained an abnormally elevated concentration of bacteria, especially anaerobes [44,45]. A restriction of the MAM biodiversity similar to that observed in patients with CD has been found such as reduction of Firmicutes and an overrepresentation of *Enterobacteriaceae* [19,25 44 45 54 55 56]. A decreased abundance of the genera *Bilophila* and *Desulfovibrio* was evident at the inflamed site of UC patients compared to the corresponding site of non-IBD controls, whereas a decreased amount of *Bilophila* genera and it's species (*B.wadsworthia*) was detected in the faecal microbiota of CD patients [35,57,58]. Moreover, an age-related reduction of the *Neisseria* genera bacteria was reported in inflamed sites when compared to non-inflamed ones and salivary microbiota of UC patients [12,13,15,47–49,31,35,39,50].Walujkar *et al.* suggested an increased abundance of *Stenotrophomonas, Ochrobactrum and Achromobacter* genera in UC patients as compared to the same patients during remission stage [46]. Finally, Proteobacteria phyla displayed also an age-related patterns [25].

(Fig 2)

Other phyla

Finally, a decreased in abundance of Verrucomicrobia (*Akkermansia*) and Fusobacteria (*Leptotrichia*), was reported at the inflamed colonic mucosal sites of CD and UC patients compared to the corresponding site of non-IBD controls. However, further investigation concerning an eventual association between *Leptotrichia* and UC is necessary [12,31,32,35,59–61].

In summary, among the 56 available studies on IBD, differential abundance of 40 bacterial species has been reported, 15 were specifically found in CD studies while only 16 species reported in UC studies. These variations mainly concerned Firmicutes, Proteobacteria and Bacteroidetes.

Table 1.a: Bacteria associated with inflammatory bowel disease analysed from biopsy samples.

Author	Methods	Sample origins	Study Cohort	Study Cohort characteristics at the time of sampling			*Major findings*
				Gender (no. M/no. F)	Mean age (range)	Geo. Origin	
Seksik, P. et al *2005*	▪ TTGE of 16S rRNAs	▪ Biopsy samples	▪ 15 CD	(6/9)	▪ 37.6 ▪ (21–63)	France	No bacterial species was found to be specifically associated with CD ulceration, and ulceration did not qualitatively modify the dominant associated microbiota
Ott, SJ. et al., *2004*	▪ 16S rDNA based SSCP fingerprint	▪ Biopsy samples	▪ 26 CD ▪ 31 UC ▪ 15 Inflammatory controls ▪ 31 Non-inflammatory controls	▪ (9/17) ▪ (18/13) ▪ (6/9) ▪ (10/21)	▪ 35 (16–56) ▪ 44 (23–74) ▪ 50 (20–82) ▪ 52 (26–74)	N/A	- *Bacteroides, Prevotella* **(↓IBD)**
Morgan, XC. et al., *2012*	▪ 16S rRNA-sequencing ▪ WGS	▪ Biopsy samples	▪ 121 CD ▪ 75 UC ▪ 8 Indeterminate ▪ 27 Controls	▪ (49/72) ▪ (38/37) ▪ (3/5) ▪ (12/15)	▪ 38 (35-41) ▪ 42 (38-45) ▪ 27(14-41) ▪ 36 (30-42)	USA	- *Prevotella, Streptococcus, Catenibacteria* **(↓UC)** - *Roseburia, Ruminococcus* **(↓CD)** - *Lactobacillus, Acidaminococcus, Veillonella, Shigella, Aeromonas, Fusobacterium, Shigella* **(↑CD)** - *Asteroleplasma, Porphyromonas, Bifidobacterium, Faecalibacterium, Coprococcus* **(↓IBD)**
Ananthakrishnan, AN. et al. *2017*	▪ Metagenomic sequencing	▪ Biopsy samples	▪ 42 CD ▪ 43 UC	N/A	N/A	N/A	- *Roseburia inulinivorans, Burkholderiales* species **(↑CD at 14 weeks remission)**
Frank, D. N. et al *2007*	▪ 16S rRNA sequencing	▪ Biopsy samples	▪ 68 CD ▪ 61 UC ▪ 61 Non-IBD Controls	N/A	▪ 35 (21-49) ▪ 38 (22-54) ▪ 36 (23-49)	N/A	- *Bacteroides (B. thetaiotaomicron),Lachnospiraceae* **(↓IBD)** - *Actinobacteria, Proteobacteria* **(↑IBD)**
Willing, BP. et al., *2010*	▪ T-RFLP ▪ Cloning and 16S rRNA Sequencing	▪ Biopsy from 5 locations between the ileum and rectum	▪ 6 L1-CD ▪ 8 L2-CD ▪ 6 Controls	▪ (3/3) ▪ (6/2) ▪ (3/3)	Born between (1936-1986)	N/A	- *F. prausnitzii* **(↓L1-CD)** - *E.coli* **(↑L1-CD)**
Png, C. W. et al. *2010*	▪ 16S rRNA qPCR ▪ In vitro mucus degradation test	Biopsy samples	▪ 26 CD ▪ 20 UC ▪ 20 Controls	▪ (6 / 20) ▪ (13 / 7) ▪ (9 / 11)	▪ 38 (19 – 74) ▪ 48 (24 – 71) ▪ 53 (22 – 84)	N/A	- *R. gnavus R. torques* **(↑CD/UC)** - *Akkermansia muciniphila,* **(↓CD/UC)**
Hansen, R. et al *2012*	▪ 16S rRNA RT-PCR and pyrosequencing	▪ Colonic mucosa biopsy samples	▪ 13 CD ▪ 12 UC ▪ 12 Controls	▪ (10/3) ▪ (9/3) ▪ (8/4)	▪ 13 (8- 17) ▪ 13 (9 - 16) ▪ 12 (7- 16)	Scotland, UK	- *Faecalibacterium* **(↑CD)**
Wang, M. et al *2007*	▪ 16S rRNA sequencing	▪ Colonic biopsy samples	▪ 1 UC (colonic microbiota)	▪ (0/1)	▪ 12-year-old	N/A	- *Enterobacteriaceae, Bacteroides fragilis, F. prausnitzii-like, Pseudomonas aeruginosa* **(↑UC)**

Rehman, A. et al *2016*	▪ 16S rRNA pyrosequencing	▪ Mucosal biopsy samples	▪ 27 CD (10 Ger.; 8 Lith.; 9 Ind.) ▪ 30 UC (10 Ger.; 10 Lith.; 10 Ind.) ▪ 30 Controls (10 Ger.; 9 Lith.; 11 Ind.)	▪ Ger. (14/16) ▪ Lith. (10/17) ▪ Ind. (21/19)	▪ Ger.(16-63) ▪ Lith.(19-81) ▪ Ind. (17-67)	▪ Germany ▪ Lithuania ▪ India	- *Firmicutes* **(↓Ger. Controls /CD Lith. Ind.)** - *Bacteroidetes* **(↑UC)** - *Proteobacteria* **(↑CD Lith./Ind.)**
Hirano, A. et al. *2018*	▪ 16S rRNA sequencing	▪ Mucosal biopsies samples	▪ 14 UC ▪ 14 Non-IBD (Controls)	▪ (6/8) ▪ (8/6)	▪ 45 (17-67) ▪ 59 (41-73)	N/A	- *Cloacibacterium, Neisseria genus, Tissierellaceae family,* **(↑inflammed site UC compared to non-inflamed site UC)** - *Prevotella, Eubacterium, Neisseria, Leptotrichia, Bilophila, Desulfovibrio, Butyricimonas* **(↓UC corresponding site of non-IBD controls).** - *Prevotella, Butyricimonas* **(↓UC patients compared with the corresponding site in non-IBD controls)**
Chiodini, R. J. et al. *2015*	▪ Deep 16S rRNA sequencing	▪ Ilea mucosal and submucosal biopsy samples	▪ 20 CD ▪ 15 Non-IBD (Controls)	(9/11) (4/11)	▪ 41 (24-66) ▪ 59 (32-88)	USA	- Desulfovibrionales **(↑CD in the subjacent submucosa as compared to the parallel mucosal tissue including)** - *Ruminococcus spp.***,** *Oscillospira spp.***,** *Pseudobutyrivibrio spp., Tumebacillus spp.***,** *Propionibacterium spp.***,** *Cloacibacterium spp.***, Proteobacteria (***Parasutterella spp. , Methylobacterium spp***) (↑CD)**
Swidsinski, A. et al. *2002*	▪ 16S rRNA sequences ▪ FISH 3 group-specific FISH probes	▪ Colonic biopsy samples	▪ 54 CD ▪ 119 UC ▪ 104 In.C ▪ 28 S.l.C ▪ 40 Controls	▪ (25/29) ▪ (52/67) ▪ (46/58) ▪ (16/12) ▪ (23/17)	▪ 35 (17-86) ▪ 45 (1786) ▪ 46 (19-81) ▪ 37(17-70) ▪ 50 (26-77)	Berlin , Germany	No principal difference in the composition of the mucosal flora in IBD patients and controls. Species isolated from the washed mucosa were of faecal origin in all groups. Proportion of *Enterococci/Streptococci, Clostridia, Peptostreptococci* , Eubacteria *were lower* - Proportion of Collinsella *aerofaciens* **or** Propionibacte *ria* **higher than usually found in faecal specimens**
Swidsinski, A. et al. *2005*	▪ FISH 14 group-specific FISH probes	▪ Mucosal Biopsy samples	▪ 20 CD ▪ 20 UC ▪ 20 IBS ▪ 10 IBD + antibiotics ▪ 20 Controls	▪ (11/9) ▪ (9/11) ▪ (6/14) ▪ (4/6) ▪ (7/13)	▪ 33 ▪ 45 ▪ 48 ▪ 40 ▪ 47	N/A	An adherent mucosal biofilm mainly composed of *Bacteroides fragilis* is a prominent feature in patients with IBD, while biofilm composed of *Eubacterium rectale* group in IBS.
Walujkar, SA. et al., *2018*	▪ 16S rRNA gene-based sequencing	▪ Colon biopsy samples	▪ 12 UC ▪ 7 Non-IBD (Controls)	▪ N/A	▪ (30- 41) ▪ (37-54)	Maharashtra, India	*Stenotrophomonas, Ochrobactrum, Achromobacter* **(↑UC)**
Kotlowski, R. et al. *2007*	▪ RISA ▪ DNA sequencing	▪ Biopsy samples	▪ 13 CD ▪ 19 UC ▪ 15 Controls	N/A	N/A	Canada	*Enterobacteriaceae* **(↑IBD)**
Sokol, H. et al. *2007*	▪ TTGE	▪ Biopsies samples	▪ 3 Proctitis ▪ 7 Left-sided colitis	N/A	N/A	N/A	*E.coli* subdominant bacteria
Zhang, M. et al. *2007*	▪ DGGE analysis	▪ Mucosal biopsy samples	▪ 24 UC	▪ (9/15)	▪ 40 (16–72)	China	- *Lactobacilli, Clostridium leptum* subgroup were significantly different

Author	Methods	Sample origins	Study Cohort	Patients characteristics at the time of sampling			Major findings
				Gender (no. M/no. F)	Mean age (range)	Geo. Origin	
Scanlan, PD. et al., *2006*	▪ 16S rRNA sequencing DGGE	▪ Faecal samples	▪ 11 CD (Remission) ▪ 5 CD (Relaps) ▪ 18 Controls	▪ (7/3) ▪ (2/3) ▪ (10/8)	40 (25–70) 46 (25–54) 36 (25–51)	N/A	Clostridiales order species
Hourigan, SK. et al. *2015*	▪ 16S rRNA sequencing ▪ FISH 5group-specific FISH probes	▪ Faecal samples ▪ Rectal biopsies	▪ 6 CD ▪ 33 UC ▪ 14 Controls	(6/8)	51 (19–59)	N/A	↓ Clostridiales order species -*E.coli*, *Clostridia* **(↑A-UC)** -E. coli **(↑CD)**
Gevers, D. et al., *2014*	▪ 16S rRNA-sequencing ▪ **WGS**	Faecal samples	▪ 447 CD ▪ 221 Controls	N/A	(<17)	North America	- *Odoribacter, Roseburia, Faecalibacterium* **(↓IBD/CD/UC)** - *Bifidobacterium*, **(↓IBD, ↑UC)** - *Coprococcus* (↓IBD/CD) - *Escherichia, Shigella* **(↑IBD)** - *Lactobacillus* **(↑IBD/CD)** - *Ruminococcus, Clostridium, Eubacterium*

between the ulcerated and the nonulcerated regions
- It also was noted that for *Lactobacilli*, the composition

Table 1.b:Bacteria associated with inflammatory bowel disease analysed from faecal samples.

							(↓CD) - *Enterococci* **(↑CD)**
Hall, AB. et al., 2017	▪ Metagenomic sequencing	▪ Faecal samples	▪ 9 CD ▪ 10 UC ▪ 1 Indeterminate Colitis ▪ 12 Controls (3 with Gastrointestinal symptoms)	N/A	N/A	N/A	- *R.gnavus* **(↑IBD)**
Kaakoush, NO . et al. *2012*	▪ High-throughput sequencing of 16S rRNA	Faecal samples	▪ 19 L1/L4 CD ▪ 21 Controls	▪ (12/7) ▪ (13/8)	▪ 12 (11-15) ▪ 10 (9-14)	Sydney, Australia	- *Oscillospira* **(↓CD)**
Aomatsu, T. et al 2012	▪ 16S rRNA Sequencing T-RFLP analysis	▪ Faecal samples	▪ 10 CD ▪ 14 UC ▪ 27 Controls	▪ (4/6) ▪ (5/9) ▪ (12/15)	▪ (8-18) ▪ (8-15) ▪ (1-5)	N/A	- *Parabacteroides, Bacteroides, Roseburia, Coprococcus , Blautia, Dorea, Ruminococcus, Oscillospira, Eubacteria, Dialister, Sutterella, Bilophila* **(↓CD)** - *Lactobacillus,Streptococcus, Enterococcus, Gemella, Haemophilus (spp.) , Eikenlla* **(↑CD)** - *Bacteroides* **(↓IBD)**
Machiels, K. et al 2014	▪ DGGE of 16S rRNA ▪ Metabolites quantification by gas chromatography–mass spectrometry	▪ Faecal samples	▪ 127 UC ▪ 87 Controls	▪ (74/53) ▪ (39/48)	▪ 43 (32-55) ▪ 42 (30-53)	Belgium	*Roseburia (R. hominis), Clostridium, Butyricimonas, F. prausnitzii* **(↓IBD : UC)**
Duboc, H. et al *2013*	▪ 16S rRNA qPCR	▪ Faecal samples	▪ 7 A-CD ▪ 5 R-CD ▪ 16 A-UC ▪ 14 R-UC ▪ 29 Controls	▪ (3/4) ▪ (2/3) ▪ (7/9) ▪ (9/5) ▪ (11/18)	▪ 38 (19-57 ▪ 42 (23-61) ▪ 36 (22-50) ▪ 38 (26-50) ▪ 35 (21-49)	N/A	- *Clostridium (C. leptum) , Blautia (B. coccoides)* **(↓IBD)** - *F. prausnitzii* **(↓CD)** - *Escherichia(E.coli)* **(↑IBD)**
Fujimoto, T. et al 2012	▪ 16S rRNA qPCR ▪ T-RFLP	▪ Faecal samples	▪ 47 CD ▪ 20 Controls	▪ (31/16) ▪ (14/6)	▪ 36 (26-45) ▪ 45 (28/62)	Japon	*F. prausnitzii* **(↓CD)**
Pascal, V et al. *2017*	▪ 16S rDNA sequencing	▪ Faecal samples	▪ Spanish cohort (34 CD ,33 UC, 111 Controls) ▪ Belgian cohort (53 CD)	▪ (21/13) ▪ (25/28)	▪ 34 (18–58) ▪ 41 (27–53)	▪ Spain ▪ Belgium	- *Faecalibacterium, Peptostreptococcaceae, Anaerostipes, Methanobrevibacter, Christensenellaceae, Collinsella* **(↓CD)** - *Fusobacterium, Escherichia* **(↑CD)**
Swidsinski, A. et al *2008*	▪ Fluorescence in situ hybridization (FISH)	▪ Faecal samples	▪ 82 CD ▪ 105 UC ▪ 32 Controls	N/A	▪ 34.8 (17-78) ▪ 41.2(18-84) ▪ 40 (18-60)	Germany	- *F.prausnitzii,* **(↓CD/↑UC)** - *Enterobacteriaceae* **(↑ CD/UC)** - *Enterobacteriaceae* **(↓CD/↑UC)** - *Eubacterium hallii, E. cylindroides bacteria* **(↓CD)** - *Bifidobacteria, Atopobium* **(↑UC)**
Sokol, H. et al. *2009*	▪ 16S rRNA	▪ Faecal samples	▪ 22 A-CD ▪ 10 R-CD ▪ 13 A-UC	▪ (7/15) ▪ (4/6) ▪ (8/5)	▪ 37 (34 - 41) ▪ 40 (35 – 44) ▪ 40 (37 – 44)	N/A	- *F.prausnitzii* **(↓R-IBD/ IC/ A-CD/A-UC)**

			▪ 4 R-UC ▪ 8 IC ▪ 27 Controls	▪ (1/3) ▪ (5/3) ▪ (11/16)	▪ 35 (31 – 40) ▪ 34 (29 - 39) ▪ 36 (35- 37)		- *Bifidobacterium* **(↓IC)**
Sabino, J. et al *2016*	▪ 16S rDNA sequencing	▪ Faecal samples	▪ 18 PSC only ▪ 27 PSC-UC ▪ 21 PSC-CD ▪ 30 CD ▪ 13 UC ▪ 52 Controls	▪ (10/8) ▪ (20/7) ▪ (18/3) ▪ (15/15) ▪ (4/9) ▪ (49/3)	▪ Median age 49 (15.25) ▪ Median age 43 (14) ▪ Median age 49 (17) ▪ Median age 52 (14.25) ▪ Median age 50 (28) ▪ Median age 51.5 (17)	Belgium	*Enterococcus, Fusobacterium, Lactobacillus* **(↑PSC only/ PSC-UC/PSC-CD)**
Bajer, L. et al. *2017*	▪ 16S rRNA Sequencing	▪ Faecal samples	▪ 32 PSC-IBD ▪ 31 Controls	▪ (17/15) ▪ (13/18)	▪ 40 (20-71) ▪ 44 (22-72)	Prague	- *Rothia, R. mucilaginosa, Fusobacteriaceae* **(↑PSC-IBD)** - *Adlercreutzia, Ruminococcus* **(↓PSC-IBD)** - *Butyricicoccus pullicaecorum sp* **(↓UC)**
Eeckhaut, V. et al. *2013*	▪ 16S rRNA sequencing ▪ Genus-specific qPCR	▪ Faecal samples	▪ 51 CD ▪ 91 UC ▪ 88 Controls	▪ (23/21) ▪ (54/37) ▪ (39/49)	▪ Median age 39 ▪ Median age 44 ▪ Median age 41	N/A	*Butyricicoccus* **(↓CD/UC)**
Knoll, R. L. et al. *2016*	▪ Metagenomic analysis	▪ Faecal samples	▪ 6 CD ▪ 6 UC ▪ 12 Controls	▪ (3/3) ▪ (2/4) ▪ (6/6)	▪ (11-17) ▪ (11-16) ▪ (8-20)	N/A	- *F. prausnitzii, E. rectale* **(↓CD/UC)** - *E.coli, F.nucleatum, E. coli, F. nucleatum* **(↑IBD)**
Andoh, A. et al. *2011*	▪ 16S rRNA sequencing ▪ T-RFLP ▪ PCR ▪ T-RFL	▪ Faecal samples	▪ 31 CD ▪ 31 UC ▪ 30 Controls	▪ (16/15) ▪ (15/16) ▪ (12/18)	▪ 30 ▪ 33 ▪ 35	N/A	- *Clostridium* **(↓IBD)**
Sokol, H. et al. *2006*	▪ 16S rDNA and rRNA PCR TTG	▪ Faecal samples	▪ 9 UC ▪ 9 Controls	▪ (5/4) ▪ (6/3)	▪ 39 (25-69) ▪ 43 (23-69)	N/A	- *Clostridium coccoides* **(↓UC)**
Sokol, H. et al. *2006*	▪ FISH 6 group-specific FISH probes ▪ Flow cytometry	▪ Faecal samples	▪ 13 CD ▪ 13 UC ▪ 5 IC ▪ 13 Controls	▪ (2/11) ▪ (7/6) ▪ (2/3) ▪ (7/6)	▪ 37(24–50) ▪ 41(28–54) ▪ 29(25–33) ▪ 40(25–56)	N/A	- *C. coccoides* **(↓UC)** - *C. leptum* **(↓CD)** - *Bacteroides* **(↑IC)**
Giaffer, MH. et al. *1991*	▪ 16S rRNA quantitative and semi-quantitative bacterial culture techniques	▪ Faecal samples	▪ 22 A-CD ▪ 20 Quiescent CD ▪ 18 A-UC ▪ 19 Quiescent UC ▪ 21 Controls	▪ (6/16) ▪ (5/15) ▪ (8/10) ▪ (7/12) ▪ (11/10)	▪ 38 ▪ 50 ▪ 37 ▪ 50 ▪ 35	N/A	*Lactobacillus, Bifidobacteria* **(↓CD)**
Seksik, P. et al *2003*	▪ 16S rDNA quantitative dot blot hybridization ▪ TTGE of 16S rDNA	▪ Faecal samples	▪ 8 A-CD ▪ 13 R-CD ▪ 16 Controls	▪ (1/7) ▪ (3/6) ▪ (7/9)	▪ 35 (16–68) ▪ 47 (32–62)	N/A	- *Enterobacteria* **(↑CD)**
Schwiertz, A. et al *2010*	▪ 16S rRNA sequencing	▪ Faecal samples	▪ 21 A-CD ▪ 19 R-CD ▪ 13 A-UC ▪ 16 R-UC ▪ 25 Controls	N/A	14 (5-19)	N/A	- *Bifidobacteria* **(↓IBD)** - *Faecalibacterium* **(↓CD)**

Thorkildsen, L. T. et al. *2013*	▪ 16S rRNA sequencing ▪ MCR	▪ Faecal samples	▪ 30 CD ▪ 33 UC ▪ 3 IBDU ▪ 33 Non-IBD	▪ (10/20) ▪ (17/16) ▪ (1/2) ▪ (14/19)	▪ 33 (21-53) ▪ 34 (17-62) ▪ 42(35-53) ▪ 33 (20-56)	Norway	- *Escherichia* **(↑CD)** - *Shigella* **(↑IBD/CD)**
Martinez-Medina, M. et al. *2006*	▪ 16S rRNA gene sequencing ▪ PCR-DGGE ▪ BLAST database	▪ Faecal samples	▪ 19 CD ▪ 2 UC ▪ 1 Ischemic colitis ▪ 15 Controls	▪ (9/10) ▪ (1/1) ▪ (0/1) ▪ (5/11)	▪ (33-41) ▪ (29-34) ▪ 27 ▪ (43-50)	N/A	- *Clostridium spp Ruminococcus Escherichia coli* **(↑CD)** - *γ-proteobacteria occasionally, in CD mucosal microbiota*
Jia, W. et al. *2012*	▪ DNA 454 sequencing ▪ DGGE ▪ In-depth sequencing ▪ NGS	▪ Faecal samples	▪ 20 CD ▪ 14 UC ▪ 21 IBS ▪ 18 Controls	N/A	N/A	England	- *B. wadsworthia, Desulfovibrio piger* **(↑CD/UC/IBS)**
Vigsnæs, L. k. et al. *2012*	▪ DGGE	▪ Faecal samples	▪ 6 R-UC ▪ 6 UC ▪ 6 Controls	N/A	N/A	Danemark	- *Lactobacillus spp. and Akkermansia (A. muciniphila)* **(↓UC)**
Michail S. et al., *2012*	▪ PCR of bacterial 16S rRNA ▪ Microarray hybridization	▪ Faecal samples	▪ 27 UC ▪ 26 Controls	▪ (17/10) ▪ (14/12)	▪ (10-17) ▪ (10-16)	N/A	- *Clostridia* **(↓UC)** - *γ-proteobacteria* **(↑UC)**
Papa, E. et al., *2012*	▪ DNA 454 pyrosequencing ▪ Sanger sequencing	▪ Faecal samples	▪ 23 CD ▪ 43 UC ▪ 1 IBDU ▪ 24 Controls	▪ (13/10) ▪ (21/22) ▪ (1/0) ▪ (10/14)	▪ 15 (3–20) ▪ 14 (4–24) ▪ 10 (3–17) ▪ 14	N/A	
Varela, E. et al. 2013	▪ qPCR	▪ Faecal samples	▪ 116 R-UC ▪ 29 First degree relatives ▪ 31 Controls	▪ (55/61) ▪ (13/16) ▪ (17/14)	▪ 40 (32–46) ▪ 37 (27–54) ▪ 32 (23–41)	▪ Spain	- *F.prausnitzii* **(↓UC/relatives/ ↑R-UC)**

Table 1.c : Bacteria associated with inflammatory bowel disease analysed from both faecal and biopsy samples.

Author	Methods	Sample origins	Study Cohort	Patients characteristics at the time of sampling			Major findings
				Gender (no. M/no. F)	Mean age (range)	Geo. Origin	
Willing, BP. et al., *2010*	▪16S rRNA-sequencing	▪ Faecal samples ▪ Mucosal samples	▪ 15 L1 ▪ 12 L2 ▪ 2 L3 ▪ 15 UC ▪ 35 Controls	▪ (7/8) ▪ (6/6) ▪ (0/2) ▪ (7/8) ▪ (10/25)	▪ 53 (20–70) ▪ 47 (20–70) ▪ 46 (42–49) ▪ 54 (30–69) ▪ 52 (30–70)	Swedish	- *Bacteroides* **(↑IBD)** - *Prevotella* **(↓UC)** - *Lactobacillus, R.gnavus, Veillonella* **(↑CD)** - *Faecalibacterium* **(↓CD)**
Sokol, H. et al.*2008*	▪ qPCR of F. prau	▪ Mucosal biopsy and ▪ Faecal samples	▪ 98 CD	N/A	N/A	N/A	- *F. prausnitzii, C. leptum group* **(↓L1-CD)**
Chen, L. et al. *2014*	▪ 16S rRNA 454-pyrosequencing	▪ Biopsies different locations (Ileum, Cecum and Rectum) ▪ Faecal samples	▪ 26 CD ▪ 46 UC ▪ 21 Controls	▪ (17/9) ▪ 30/11) ▪ (10/11)	▪ 30 (18-46) ▪ 42 (19-70) ▪ 28 (22-40)	China	- *Faecalibacterium***(↓CD/ ↑UC)** - *The abundance of the genus Escherichia-Shigella* **(↑CD/UC)** - *Enterococcus, ,* **(↑IBD).**
Vermeiren, J. et al. *2012*	▪ M-SHIME *in vitro* dynamic gut model ▪ DGGE of 16S rRNA	▪ Luminal and mucosal biopsy samples ▪ Faecal samples	▪ 6 UC ▪ 6 Controls	N/A	▪ 41 (33-78) ▪ 27 (25-34)	N/A	- *Clostridium cluster XIVa, Roseburia spp., members of the C. coccoides/E. rectale group, F. prausnitzii, a species of the C. leptum group, Bacteroides/Prevotella* **(↓UC)**
Wang, W. et al., *2014*	▪ 16S rRNA-sequencing	▪ Faecal samples ▪ Biopsy samples	▪ 25 CD ▪ 41 UC ▪ 21 Controls	▪ (12/9) ▪ (30/11) ▪ N/A	▪ 30 (17-51) ▪ 43 (19-74) ▪ N/A	China	- *Lactobacillus* **(↑IBD)**

A/R-CD / UC = Active / Remission Crohn Disease / Ulcerative Colitis; CD= Crohn disease, DGGE= Denaturing gradient gel Electrophoresis; FISH = Fluorescence in situ hybridization; IBD= Inflammatory bowel disease; IBDU = Inflammatory bowel disease unclassified; IBS = Irritable bowel syndrome; IC = Infectious Colitis; L1-CD= Ileum localized CD(Montreal classification); L1/L4 CD = Ileum localized CD with upper-gut involvement (Montreal classification); L2-CD= CD with primarily Colonic involvement (Montreal classification); L3-CD= Ileocolonic Crohn's Disease (Montreal classification); MCR= Multivariate curve resolution; N/A = Not available; NGS = Next generation sequencing; PCR= Polymerase Chain Reaction; PSC = Primary sclerosing cholangitis; qPCR = quantitative Polymerase Chain Reaction; RISA = Ribosomal intergenic spacer analysis; RT-PCR = Reverse Transcription - Polymerase Chain Reaction; SSCP = Single Strand Conformation Polymorphism; S.l.c = Self-limiting colitis (s.l.c); T-RFLP = Terminal restriction fragment length polymorphism; TTGE= Temporal temperature gradient gel electrophoresis; UC = Ulcerative Colitis; In.C = Indeterminate colitis; WGS = Whole Genome Shotgun

A.2. Gut bacterial changes reported in chronic rheumatic diseases patients

A total of twenty-one studies, enrolling 993 CRD patients analyzing the gut microbiota by 16S rRNA gene sequencing from faeces. Breban *et al*. have demonstrated that β-diversity analysis, which evaluates the shared diversity between different microbiomes in terms of various ecological distances, showed a microbiota composition significantly different between the RA, SpA and healthy subjects (HS) groups. Both SpA and RA patients differed from HSs as well as SpA from RA patients . This study showed also that α-diversity, which evaluates the species' richness and evenness within the microbiota, assessed by the number of observed species was significantly decreased in both SpA and RA patients, as compared with HSs[62,63]. In ankylosing spondylitis (AS) patients, the diversity of the gut microbiome was similar to HSs at the genus level but was significantly higher in the controls at the species level [64].

Firmicutes phyla

Concerning the Firmicutes phylum, several bacteria from the *Lachnospiraceae* family, including *Ruminococcus* (*R. gnavus* sp.), *Dorea*, *Coprococcus* and *Blautia* genera are overabundant in SpA [62]. Increased amount of several *Blautia* and *Ruminococcus* could characterize HLA-B27^{+} siblings [62]. Likewise, inflamed ileal biopsies of SpA patients revealed an increase in the *Dialister* genus which could be a microbial marker of disease activity [65,66]. In contrast, SpA patients seemed to present a decreased amount of *Roseburia* species [62]. Concerning RA patients, a fewer Firmicutes of the *Ruminococcaceae* family but an increase in *Lactobacillus* species and *Faklamia* have been observed [62,67]. A study by Picchianti-Diamanti et al. characterized the gut microbiota of RA patients on different immunosuppressants treatment strategies (ETN, MTX, or ETN plus MTX) and compared it with that of treatment-naïve patients. The drop in Proteobacteria caused by ETN which in general are abundant in both intestinal and extra-intestinal inflammatory diseases [68]. Moreover, a decrease in *Clostridiaceae* was observed upon ETN treatment which were previously found enriched in patients with RA and IBD-associated arthropathy [69]. In patients treated with MTX, analysis revealed a significant decrease in Enterobacteriales [67].

Liu et al. reported that RA patients, compared to HSs, exhibited an increased bacterial diversity within *Lactobacillus* community with increase *in L.salivarius* and *L.iners* [62,70,71] for instance. The analysis of faeces from RA patients have demonstrated the presence of a large cluster including Firmicutes bacteria belonging to *Lachnospiraceae* and *Clostridiaceae* (*Clostridium*) family, as well as small clusters containing strains from the *Lactobacillus* and

Ruminococcus genera[70–73] . In the RA patients' gut, a decrease of bacteria from the *Veillonellaceae* family was observed [72,74]. In contrast to SpA patients, PsA patients showed depletion in *Coprococcus*, *Ruminococcus*, *Clostridium* and *Pseudobutyrivibrio* compared to HSs [62,74–76]. Finally, SpA patients exhibited a decreased fecal abundance of *F.prausnitzii* compared to HSs. This bacterium may be, at least in part, responsible for the pathogenesis of SpA[66,77,78].

Bacteriodetes phyla

There is a significant enrichment of the *Prevotellaceae* species, and more particularly of *Prevotella copri*, within the Bacteriodetes phylum, in intestinal microbiota of patients with new-onset RA, compared to chronic RA patients and HSs [79–81]. This bacterium is relatively scarce in the general population. In addition, *Bacteroides* genera counts were lower in the same group, while being higher in SpA patients [79,66,72]. However, *P. copri* decreased in the gut of RA patients along with disease chronicity [80]. Breban *et al.* also demonstrated that SpA and RA patients have decreased populations of *Prevotellaceae* and *Paraprevotellaceae* genera compared to HSs [62]. However, in AS patients, *Prevotellaceae* are more abundant in terminal ileal biopsy samples [77]. Furthermore, a quantitative metagenomics study has shown that the microbial communities in the AS cases were characterized by a higher abundance of *Prevotellaceae* genera (*Prevotella copri*) compared to HSs [64]. Other bacteria from the Bacteroidetes phylum, such as *Porphyromonas*, were shown to be decreased in RA patients while being increased in terminal biopsies of AS patients [77,82].

Actinobacteria phyla

Regarding the Actinobacteria phylum, which is a low-abundant one, patients with RA or SpA had a higher amount of bacteria from the *Coriobacteriaceae* family and especially of the *Bifidobacterium* genus, including *B. bifidum* species than HSs [62,66]. However, RA patients are also characterized by an increase of *Corynebacterium* species [62]. The metagenomic analysis and 16S sequencing have additionally brought into light the presence of the bacteria *Gordonibacter pamelaeae*, *Eggerthella lenta* and *Collinsella* in RA patients[63,64, 72]. The latter could contribute to the increased permeability of the gut and enhanced production of pro-inflammatory cytokines [66]. In SpA patients, an overabundance of *Collinsella*, *Rothia* and *Actinomyces* genera was reported [63,64,76].

Proteobacteria phyla

The Proteobacteria phylum is more abundant in RA patients than in HSs, concerning more specifically the *Klebsiella* and *Bilophila* genera from *Enterobacteriaceae*,

Author	Methods	Samples origins	Study Cohort	Patients characteristics at the time of sampling			Major findings
				Gender (no. M/no. F)	Mean age (range)	Geo. Origin	

Desulfovibrionaceae and *Succinivibrionaceae* families [62]. In SpA patients there is a decrease of *Citrobacter*, *Enterobacte*r and *Erwinia genera* [71,73,76]. The latter was particularly reduced in the HLA-A24 positive group of patients. In contrast, an overabundance of *Neisseria ge*nera was reported SpA patients [64].

Other phyla

Finally, other phyla as Synergistetes, Tenericutes, Fusobacteria and Verrucomicrobia were also retrieved to be increased or decreased in RA and SpA patients [12,62,64,75,83]. (Fig 2)

In summary, among the available studies on CRD (n= 21), 33 bacterial species were reported in CRD, among those 17 were specifically reported in SpA studies while only 9 species reported in RA studies. Variations mainly concerned *Firmicutes*, *Bacteroidetes* and *Actinobacteria* phyla.

Table 2.a: Bacteria associated with chronic rheumatoid diseases analysed from faecal samples.

Breban, M. et al. *2017*	▪ 16S rRNA gene sequencing	▪ Faecal samples	▪ 86 SpA patients (74 SpA, 12 SpA+ IBD history) ▪ 28 RA ▪ 69 Controls	▪ (41/46) ▪ (6/22) ▪ (26/43)	▪ (35-63) ▪ (54-76) ▪ (27-63)	France	- *Klebsiella, Desulfovibrionacae (bilophila), Succinivibrionaceae, Synergistetes, Tenericutes* **(↑RA)** - *Bifidobacterium* **(↓ RA /↑SpA)** - *Paraprevotella* **(↓SpA)** - *Coriobactericeae, Ruminococcus, coprococcus, Dorea , Blautia* **(↑SpA)**
Picchianti - Diamanti, A. et al. *2018*	▪ NGS 16S Rrna	▪ Faecal samples	▪ 11 RA treatment naïve patients ▪ 11 RA received MTX ▪ 10 RA received ETN ▪ 10 RA received ETN+MTX ▪ 10 Controls	▪ (1/10) ▪ (2/9) ▪ (1/9) ▪ (2/8) ▪ N/A	▪ 56 ▪ 63 ▪ 60 ▪ 65 ▪ N/A	Finland	- *Lactobacillaceae, Lactobacillus (↑RA)* - *Faecalibacterium* **(↓RA)** - *Cyanobacteria phylum, Nostocophycideae ,Nostocales group* **(↑RA-ETN)** - *Deltaproteobacteria* **(↑RA-ETN/UC)** - *Clostridiaceae upon* **(↓RA-ETN)** - *Enterobacteriales* **(↓RA- MTX)**
Chen, J. et al. *2016*	▪ 16S rRNA sequencing	▪ Faecal samples	▪ 40 RA patients, ▪ 32 Controls	▪ (12/28) ▪ (6/26)	▪ 56 ▪ 53	USA	- *Eggerthella* **(↑RA)** - *Collinsella* **(↑RA/SpA)**
Wen, C. et al. *2017*	▪ Deep shotgun sequencing	▪ Faecal samples	▪ 97 AS ▪ 114 Controls	▪ (57/40) ▪ (72/42)	▪ (14-71) ▪ (23-70)	China	- *Collinsella, Prevotella copri* **(↑RA/SpA)** - *Actinobacteria, Neisseria, rothia, Actinomyces* **(↑SpA)** - *Fusobacteria, Citrobacter, Verrucomicrobia* **(↓SpA)**
Stoll, ML. et al. *2018*	▪ 16S rRNA sequencing ▪ Shotgun sequencing	▪ Faecal samples	▪ 30 ERA ▪ 19 Controls ▪ 11 SpA ▪ 10 Controls	▪ (19/11) ▪ (13/6) ▪ (4/7) ▪ (3/7)	▪ 14 (11-17) ▪ 14 (11-17) ▪ 52 (45-60) ▪ 47 (39-56)	USA	- *Bifidobacterium, Actinobacteria, Lachnospiracea* **(↑RA/SpA)** - *F. Prausnitzii* **(↓RA/SpA)**
Liu, X. et al. *2013*	▪ 16S sequencing	▪ Faecal samples	▪ 15 RA ▪ 15 Controls	▪ (3/12) ▪ (5/10)	▪ 48 ▪ 41	China	*Lactobacillus genera (Lactobacillus salivrius, L. Iners, L. ruminis)* **(↑RA)**
Maeda, Y. et al. EULAR *2012*	▪ RT-qPCR bacterial rRNA-targeted	▪ Faecal samples	▪ 37 RA patients ▪ 59 Controls	▪ (12/25) ▪ (6/53)	▪ 60 (49-71) ▪ 35 (25-45)	Japan	*L. ruminis, L.fermentum, L. reuteri, Enteroccocus* **(↑RA)**
Scher, JU. et al. *2015*	▪ 16S rRNA sequencing	▪ Faecal samples	▪ 16 SpA ▪ 17 Controls	▪ (7/9) ▪ (7/10)	▪ 47 ▪ 43	USA	*Verrucomicrobia, Pseudobutyrivibrio* **(↓SpA)**
Manasson . et al., *2018*	▪ 16S rRNA sequencing	▪ Faecal samples	▪ 32 ReA ▪ 32 Controls	N/A	(18-55)	USA	- *Rikenellaceae* **(↑SpA)** - *Pseudomonas* **(↑RA/SpA)**
Stoll, ML. et al. *2015*	▪ 16S rRNA sequencing	▪ Faecal samples	▪ 12 recent onset ERA ▪ 21 Controls	ACR meeting Abstract			*F. Prausnitzii* **(↓RA/SpA)**
Scher, JU. et al. *2013*	▪ 16S rRNA sequencing ▪ Shotgun sequencing	▪ Faecal samples	▪ 44 NORA ▪ 26 CRA ▪ 16 PsA ▪ 28 Controls	▪ (11/33) ▪ (3/23) ▪ (7/9) ▪ (7/21)	▪ 43 ▪ 50 ▪ 47 ▪ 43	USA	*Prevotella copri* **(↑RA/SpA)**
Maeda, Y. et al. *2016*	▪ 16S rRNA sequencing ▪ Shotgun sequencing	▪ Faecal samples	▪ 17 RA ▪ 14 Controls	▪ (3/14) ▪ (0/14)	▪ 64 (51-69) ▪ 53 (44-70)	Japan	*Prevotella copri* **(↑RA/SpA)**
Vaahtovuo , J. et al. *2008*	▪ Flow cytometry ▪ 16S rRNA hybridization ▪ DNA-staining	▪ Faecal samples	▪ 51 RA	(9/42)	▪ 57 (44- 70)	Finland	*Porphyromonas* **(↓RA/SpA)**
Stoll, M. L. et al. *2014*	▪ 16S rRNA sequencing	▪ Faecal samples	▪ 25 ERA ▪ 13 Controls	▪ (14/11) ▪ (6/7)	▪ 13 (7-19) ▪ 13 (6-18)	USA	- *F. prausnitzii* **(↓ERA)** - *Clostridium leptum group* **(↓AS)**
Stebbings, S. et al.	▪ DGGE	▪ Faecal samples	▪ 15 AS ▪ 15 Controls	N/A	N/A	N/A	*Klebsiella pneumoniae, Bacteroides vulgatus*

2002							**(↓AS)**

Table 2.b: Bacteria associated with chronic rheumatoid diseases analysed from biopsy samples.

Table 2.c: Bacteria associated with chronic rheumatoid diseases analysed from faecal and other origin samples.

Author	Methods	Samples origins	Study Cohort	Patients characteristics at the time of sampling			Major findings
				Gender (no. M/no. F)	Mean age (range)	Geo. Origin	
Tito, RY. et al. *2017*	▪ 16S rRNA sequencing	▪ Biopsy samples ileal and colonic	▪ 27 SpA ▪ 15 Controls	▪ (13/14) ▪ N/A	▪ (10-50) ▪ N/A	Belgium	*Dialister* **(↑SpA)**
Costello, ME. et al. 2016	▪ 16S rRNA sequencing	▪ Intestinal biopsy	▪ 10 HLA-B27^{+} ▪ 85 HLA-B27^{-}	ACR meeting Abstract			*Veillonellaceae* **(↓RA/SpA)**
Costello, ME. et al. 2013	▪ 16S sequencing	▪ Terminal ileal Biopsy	▪ N/A AS ▪ N/A CD ▪ N/A Controls	ACR meeting Abstract			- *Porphyromonas , F. Prausnitzii* **(↓RA/SpA)** - *Ruminococc* **(↑SpA)**

ACR = American College of Rheumatology ; AS = Ankylosing spondylitis; CRA = Chronic, treated rheumatoid arthritis; DMARD = Disease-modifying antirheumatic drug; ETN = Etanercept; EULAR = European League Against Rheumatism; ERA = Enthesitis-related arthritis; IBD = Inflammatory bowel disease; NORA = new onset untreated rheumatoid arthritis; MTX = Methotrexate; PsA = Psoriasis arthritis; RA = Rhumatoide arthritis; ReA = Reactive arthritis; SpA = Spondylo-arthritis; ; UA = Undifferentiated Arthritis; UC = Ulcerative Colitis.

Author	Methods	Samples origins	Study Cohort	Patients characteristics at the time of sampling			Major findings
				Gender (no. M/no.F)	Mean age (range)	Geo. Origin	
Zhang, X. et al. *2015*	▪ Metagenomic sequencing	▪ Faecal samples ▪ Dental samples ▪ Salivary	▪ 115 RA (21 DMARD) ▪ 97 Controls	▪ (31/84) ▪ (28/69)	▪ 50 (27-74) ▪ 43 (19-68)	China	- *Collinsella, Eggerthella, Gordonibacter pamelaeae, Clostridium, Lachnospiracea* **(↑RA)** - *Veillonellaceae* **(↓RA/SpA)**
Benham, H. et al. 2016	▪ 16S rRNA sequencing ▪ Tongue and faecal swabs	▪ Tongue and faecal swabs	▪ 116 RA ▪ 63 First-Degree Relatives ▪ 43 Controls	ACR meeting Abstract			- *Enteroccocus* **(↑RA)** - *Pseudomonas* **(↑RA/SpA)**

A.3. Differences between IBD and CRD gut microbiota

Three studies enrolling a total of 554 patients, directly compared 356 IBD patients without known arthropathy, and a total of 132 IBD with joint extra-intestinal-manifestation (EIM) patients were analysed (Table 3). One study indirectly compared three cohorts of patients,

SpA patients without IBD history (n=74) as well as SpA patients with an IBD history (n= 12),and RA patients (n=28) compared with HCs (n= 69) (Table 3)[62].

Firmicutes phyla

Amongst included studies, some pointed out important differences, including variable amount of several Firmicutes genera. For instance, the overabundance of *Veillonella* observed in CD patients contrasted with its paucity in CRD (RA, SpA) patients. Conversely, the *Eubacterium, Clostridium, Ruminococcus* and *Coprococcus* genera, that were increased in CRD (RA, SpA) patients, were decreased in patients with CD [15,12,13, 19,72,77,79,80,82,83,84]. Variation of the *Ruminococcus* genus is the most surprising since a paradoxical overabundance, especially of *R. gnavus,* has been reported in SpA patients. This increased abundance correlated positively with SpA activity whatever patients IBD history, even though IBD was inactive at the time of sampling in most of them[12,62]. In IBD, *R. gnavus* was mostly associated with the gut mucosa, which conferred to this mucolytic bacteria a possible role in the triggering or maintenance of inflammation [12,32]. Whether its lonely increase could be linked to specific genetic predispositions to SpA warrants more investigation. As for the *Dialister* genera, belonging to the same bacterial family, an increased number of sequences was observed in SpA groups whereas a decrease was found in CD patients [62]. In UC patients with a joint EIM, the *Staphylococcus* genus was found more frequently in stool cultures [85].

Bacteroidetes phyla

Variations in Bacteroidetes phylum concerned mainly two genera: *Bacteroides,* which was in increased amount in SpA patients and in reduced amount in RA and IBD groups and *Prevotella* which showed a high abundance in CRD (RA and SpA) patients and was lowered in UC patients[15,20, 63,64,66,79,80 84, 86].

Proteobacteria phyla

In the Proteobacteria phylum, the genus *Bilophila* was overabundant in RA and SpA patients while being found in reduced amounts in CD patients [12,51,62,87,88]. Dorofeyev *et al.* showed a significant abundance of *Enterobacter, Klebsiella and Proteus* genera in stools cultures from UC patients with a joint EIM, compared to HSs and UC patients without EIM [85]. In contrast, in UC a decreased amount of *Neisseria* was observed[12,13,15,47–49,31,35,39,50]. However, metagenomics studies of gut microbiome in patients with enteropathic arthritis are still lacking. Using qPCR, a relative overabundance of the *Enterobacteriaceae* family, concomitant to a reduction of the *Clostridia group XIVa* cluster, was reported in the gut microbiota in IBD patients with joint manifestations. As a whole, the *Enterobacteriaceae*

family seemed to be increased in the gut of IBD patients and this tendency is even more pronounced in those with arthropathy [89].

Actinobacteria phyla

Concerning the Actinobacteria phylum, an overabundance of *Gordonibacter pamelaeae*, *Eggerthella lenta* and *Collinsella* was observed in RA patients [63,64, 72,90]. However, an increase of *Micrococcus* genera was also characterized in MAM UC patients [46]. In SpA patients, an overabundance of *Collinsella*, *Rothia* and *Actinomyces* genera was reported [63,64,76].

Other phyla

Finally, the *Fusobacterium* phylum is more abundant in CD patients and less abundant in SpA patients[62]. In contrast, amounts of the *Tenericutes* phylum are increased in SpA patients [10,62,64].

Taken together, when considering all available studies (n=80), 40 bacterial species were reported only in IBD patients and 33 bacterial species were reported only in CRD subjects (Fig 2). Main variations were mostly observed in the *Firmicutes* phylum.

B. Similarities regarding bacterial microbiome in IBD and CRD

When comparing studies on IBD patients without known CRD *versus* studies on CRD patients without known IBD, we first observed that some dysbiotic changes share similarities between chronic IBD and chronic joint diseases, among which a lower microbial diversity and a diminished abundance of the Firmicutes phylum.

Firmicutes phyla

Amongst the Firmicutes genera, a common decreased amount was described for *Faecalibacterium* and *Roseburia* species in both IBD subtypes (CD and UC), as well as in SpA and RA patients [12,13,15,20,50,62,84]. A few studies using bacterial culture, in addition to recent molecular methods, have demonstrated an increase amount of *Lactobacillus* and *Enterococcus* in the faecal microbiota of IBD patients especially those with CD and RA patients, although others demonstrated a reduction of *Lactobacillus* in CD patients[7,12,15, 13, 47 , 30,48,49,52,70,72,84]. An overabundance of *staphylococcus* was observed in UC patients with arthritis when compared with patients without EIM and healthy population.

Proteobacteria phyla

In the Proteobacteria phylum, an overabundance of several genera was observed, such as *Klebsiela* and *Proteus* in all UC patients with arthritis. These facultative microbiota were significantly higher in these patients than in the HSs and UC patients without EIM [46,62,85,91,92]. An increase of *Pseudomonas* was recently showed by Walujkar *et al* in the MAM of UC patients as compared to the same patients during remission stage [46], as well as showed by Manasson *et al.* and Benham *et al* in patients with SpA or RA. [73,76].

Actinobacteria phyla

Concerning the Actinobacteria phylum, an overabundance of *Bifidobacterium* was reported in SpA patients, especially those with enthesitis-related arthritis (ERA), and in IBD patients notably in patients with CD [12,13,15,19,47 50,62,64,66,72, 82, 83].

Other phyla

Finally, a common decrease of Verrucomicrobia and Fusobacteria belonging species was reported in both CD and UC patients compared to non-IBD controls [10,12,31,32,35,59–61], and in RA and SpA patients [12,62,64,75,83].

In summary, variations of species belonging to Firmicutes, Proteobacteria, Actinobacteria, Verrucomicrobia and Fusobacteria phyla represent the main common trait between IBD and CRD gut microbiota. A figure depicting similarities and differences observed in bacterial species amounts in biopsy and faeces from IBD and CRD patients is proposed (Fig 2).

Table 3: Bacteria associated with inflammatory bowel disease and chronic rheumatic diseases.

Author	***Methods***	***Samples origins***	***Population studied***	***Patients characteristics at the time of sampling***			***Major findings***
				Gender (no. M/no. F)	*Mean age (range)*	*Geo. Origin*	
Muniz-Pedrogo, D.A. et al. *2018*	▪ 16S rRNA sequencing	▪ Faecal samples	▪ 25 IBD-A ▪ 66 IBD-N, ▪ 25 RA ▪ 64 Controls	▪ (11/14) ▪ (26/40) ▪ (10/15) ▪ (27/37)	▪ 49 ▪ 49 ▪ 52 ▪ 50	N/A	*Escherichia* **(↑IBD)**
Dorofeyev, A.E. et al. *2009*	▪ Culture dependent techniques	▪ Biopsies samples ▪ Faecal samples	▪ 131 Distal UC ▪ 102 Left-sided UC ▪ 86 Pancolitis ▪ 95 UC+ joint EIM	▪ (147/172) ▪ Idem ▪ Idem ▪ N/A	▪ (40-47) ▪ Idem ▪ Idem ▪ N/A	N/A	- *Bifidobacteria, lactobacilli* **and** *Escherichia coli* **(↓ UC)** - Facultative flora **(↑UC)** - *Staphylococcus , Klebsiella* **and** *Proteus* **were found more often in stool cultures (↑UC+ joint EIM)**
Kabeerdoss, J. et al. *2014*	▪ 16S rRNA sequencing	▪ Faecal samples	▪ 12 IBD + Arthropathy ▪ 12 IBD	N/A	N/A	N/A	- *Enterococcaceae, Enterococcus* and *Enterococcus faecium* **(**↑IBD+ arthropathy**)**

EIM: Extra-intestinal manifestation; IBD= Inflammatory bowel disease; IBD-A/N = IBD-associated/ without arthropathy; N/A = Not available; RA = Rheumatoid arthritis.

Conclusion and perspectives

To our knowledge, this is the first systematic review concerning evidence regarding the gut microbiota in IBD and CRD patients. Our analysis highlights the general finding that microbiota favouring proteolytic-fuelled fermentation and lactic acid-producing bacteria, are increased in both CRD and IBD inflammatory conditions while those producing butyrate are generally decrease in both diseases. Secondly, variations of gut microbiota composition in IBD patients mainly concerned *Firmicutes, Proteobacteria* and *Bacteroidetes*. Within the Firmicute phylum variations of species as *Roseburia, coprococcus, F. prausnitzii* and *Streptococcus* genera, was observed either in the mucosal-associated microbiota (MAM) of CD patients or UC patients. In terms of Proteobacteria phylum published data display a quantitative alteration in IBD CD and UC patients compared to control groups especially of *Escherichia, Shigella, Bilophila, Desulfovibrio, Neisseria, Stenotrophomonas, Ochrobactrum and Achromobacter* genera. Concerning the Bacteroidetes, variations of *Cloacibacterium, Prevotella, Butyricimonas, Parabacteroides, Elizabethkingia* genera and *Odoribacteracae* family in IBD, CD and UC patients are observed.

However, in CRD patients, variations are mainly observed in Firmicutes, Bacteroidetes and Actinobacteria phyla. Alterations of gut microbiota observed in the Firmicutes phyla included *Ruminococcus* (*R. gnavus* sp.), *Dorea, Coprococcus, Blautia* , and *Dialister* genus in RA and SpA patients. In addition alterations of *Roseburia, Lactobacillus, Faklamia, Staphylococcus, Clostridium, Pseudobutyrivibrio, F.prausnitzii* species and *Veillonellaceae* family was observed in patients compared to healthy subjects. There is a significant variations of species within the Bacteriodetes phylum, particularly of, *Bacteroides, Prevotellaceae* (*P.copri*) *Paraprevotellaceae* and *Porphyromonas* genera in RA and SpA patients compared to HSs. Regarding the Actinobacteria phylum, which is a low-abundant one, in patients with RA or SpA variations of the *Bifidobacterium* genus, including among others *B. bifidum* species, *Gordonibacter pamelaeae, Eggerthella lenta, Collinsella, Rothia* and *Actinomyces* genera was reported compared to control groups.

Another major finding of this study, is the reduction of bacterial diversity, observed in both CRD and IBD and the presence of common bacterial phyla changes. We can mention an increased abundance in *Lactobacillus, Enteroccocus, Staphylococcus, Bifidobacterium,*

Klebsiella, *Pseudomonas* and *Proteus* genera in both CRD and IBD, whereas *Faecalibacterium*, *Roseburia* genera and Verrucomicrobia, Fusobacteria phyla are decreased in both diseases.

Interestingly, experimental studies have confirmed the role of *Faecalibacterium* in immune controlled in both type of affections. First, Hablot and colleagues suggested that experimental Dextran Sulfate Sodium (DSS) induced colitis could altered the gut microbiota of mice with arthritis compared to mice with colitis alone and thus could delayed the appearance of "pro-arthritogenic" bacteria[93]. This delay is associated with a difference of microbiota composition between mice with arthritis and colitis and mice with colitis only. Members of the Firmicutes phylum are mainly affected; *Lactobacillus* genus and Clostridiales order are more present in mice with arthritis and colitis compared to mice with only colitis. Several studies showed that species from *Lactobacillus* are beneficial in DSS-induced colitis [94,95]. Thereby, *Lactobacillus sp* increase in arthritis + colitis group might play a role in the subclinical improvement as observed by the decrease in fecal lipocalin-2 level. A difference of the fecal microbiota composition is also observed between arthritis and arthritis + colitis groups. At arthritis and colitis onset, *Lactobacillaceae,* and notably *Lactobacillus R.gnavus* and S24_7 species belonging to Bacteroidales are more present in mice with arthritis and colitis compared to arthritis group. Interestingly, these groups of bacteria had been shown to be more present in mice with higher susceptibility to arthritis development [93,96].

Viladomiu and colleagues recently identified an enrichment of IgA-coated *E. coli* in CD-SpA with an adherent-invasive *E. coli* (AIEC) pathotype. Experimental models highlight two features of the host-pathogen interaction that must be considered to understand the specificity of pathogenetic mechanisms, namely, host susceptibility and strain variability[97]. CD SpA–derived AIEC protect against acute injury and death from DSS induced colitis in WT mice. Resident microbiota, including AIEC, induce colonic RORγt/Foxp3$^+$ CD4$^+$ T cells, which play an important role in restraining inflammatory colitis[98]. Consistent with a higher Enterobacteriaceae in 6-month-old infants correlated with better nutritional status [99]. Thus, in situations of nutritional sufficiency or immunocompetence, the response to Enterobacteriaceae may have coevolved to protect the host; however, persistent nutritional deficiency [99] or genetic susceptibility (modeled in IL-10–deficient and K/BxN mice) evokes maladaptive responses, which, in turn, promote more severe inflammatory Th17 disease. Likewise, this data link the shared genetic susceptibility in the IL23R locus in both CD and SpA [100] with increased systemic *E. coli* sero-reactivity and Th17 inflammatory cytokines.

These results highlight the functional implication of IgA-coated E. coli enriched in CD-SpA and identify a Th17 immunophenotype characteristic of this EIM. This mechanistic link between intestinal microbiota and systemic inflammation may underlie the clinical efficacy of sulfasalazine in peripheral joint symptoms [101]. While anti-TNFα therapy improves axial symptoms in patients with active CD [102], this data also highlight the overactivation of the IL-23/IL-17 pathway in CD patients with peripheral symptoms.

This review displays several methodological and theoretical limitations. First, heterogeneity of studied populations (in terms of age, gender and origins) and microbiota analysing methodology deeply impact gut microbiota picture. The purpose of our study, i.e. to identify similarities and differences between gut microbiome in IBD and in CRD patients, is challenging considering also the relatively small number of studies in CRD compared to IBD . Indeed, first studies analysing gut microbiota in IBD were published in 2005, whereas gut microbiota in CRD has been explored a decade later. Since the first studies, more than 4000 IBD patients have been analysed whereas only 300 for CRD.

Secondly, inconsistencies may exist among the findings from available studies due to the heterogeneity in sample size, biopsy location, local inflammation and types of samples (biopsies vs stool) that may influence the microbiota composition. Furthermore, complexity of the microbiota must be put into perspective along with current technological limitations (analysing DNAs encoding 16S RNA gene still provides only an incomplete picture of bacterial populations and some study presented here used culture dependent determination methodology).
Despite these considerations and in an effort to synthetize already published data we provide detailed tables by clinical condition and sample type as well as a figure providing an overview of the data available (figure 2).

Finally, information on the possible concomitant arthritis and IBD was not provided in some of the 80 included studies involving IBD and CRD patients. It is thus impossible to rule out the presence of subclinical joint-gut inflammation in these patients.
We can mention also the absence of healthy controls groups in certain studies or the incomplete description of clinical situation of patients (for instance patients with IBD history without information on disease activity or medication or faeces consistency score at time of sampling) that could influence gut microbiota [103].

Bacteria are not the only component of gut microbiota, fungi and virus may have a role in both diseases' initiation or severity. Bacteria and fungi could compete for the same subtracts or produce synergistically metabolites that could affects host immunity and metabolism. Only a few studies on intestinal fungal microbiota and its relationship with IBD have been conducted. Much evidence has shown that fungi and their communities may be involved in the pathogenesis of IBD, especially CD[104]. To date fungal microbiota implication in CRD has not been explored.

The enteric virome is known to be altered in patients with IBD, with specific changes assessed between UC and CD. Enormous numbers of candidate viruses have been thought to be triggering factor of arthritis, particularly of RA, but most of the evidence implicating viruses in the pathogenesis of CRD are circumstantial and inconclusive. Tantalizing observations have often been based on *in vitro* or animal studies, case reports, or studies with small sample sizes, cross-sectional designs, or without control groups.

The description of the viral, fungal, bacterial metagenomes in patients suffering from IBD and or CRD shall provide a better understanding of the interactions between the microbiome and host immunity within the joint-gut axis. The identification of specific species in well-defined categories of patients can provide valuable information, which can be translated into prognostic, diagnostic or therapeutic tools that are critically lacking for these diseases. Furthermore, such studies hold great promise for the development of future strategies aiming at early detection of relapse and at controlling/manipulating the microbiome to reduce the burden of these ailments.

In conclusion a total of 80 studies investigated bacterial microbiome in patients with IBD and/or CRD. These studies showed that some bacterial taxons seem specifically imbalanced in IBD (n=40) and CRD (n=33), while increased abundance in Firmicutes genera *Lactobacillus* and *Staphylococcus*, Actinobacteria *Bifidobacterium*, and Proteobacteria genera such as *Pseudomonas, Klebsiella* and *Proteus.* Whereas, Firmicutes phyla *Faecalibacterium*, *Roseburia* genera and Verrucomicrobia phylum are decreased in both CRD and IBD. Large and well-designed prospective studies are eagerly awaited to further elucidate the role of gut microbiome in promoting pathological inflammation within joint-gut axis.

Figures

Figure 1: Flow-diagram of identified studies.

Figure 2 Salem et al.

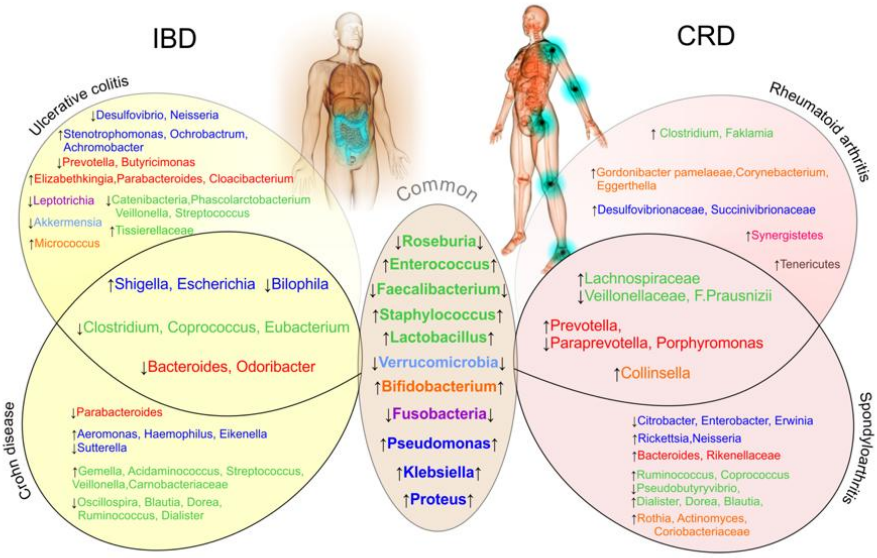

Figure 2 : Similarities and differences regarding gut bacteria between IBD and CRD patients.

Genera colours represents Phylum: ***Bacteroidetes***, ***Firmicutes***, ***Actinobacteria***, ***Proteobacteria***, ***Fusobacteria***, ***Tenericutes***, ***Synergistetes***.

↑/↓= increase / decrease in patients with IBD or CRD

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