GASTRO ENTEROLOGIA BELLUNO

Con il patrocinio di

PROGRESSI E NUOVE FRONTIERE IN
GASTROENTEROLOGIA ED ENDOSCOPIA DIGESTIVA
BELLUNO 15-16 GIUGNO 2023

Microbiota e MICI

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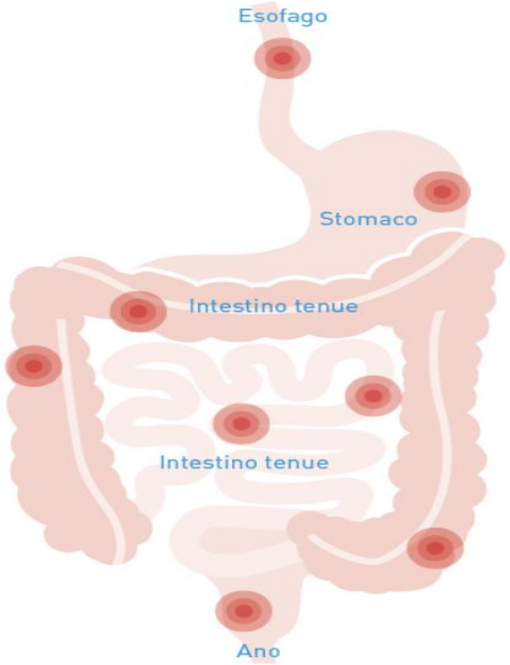
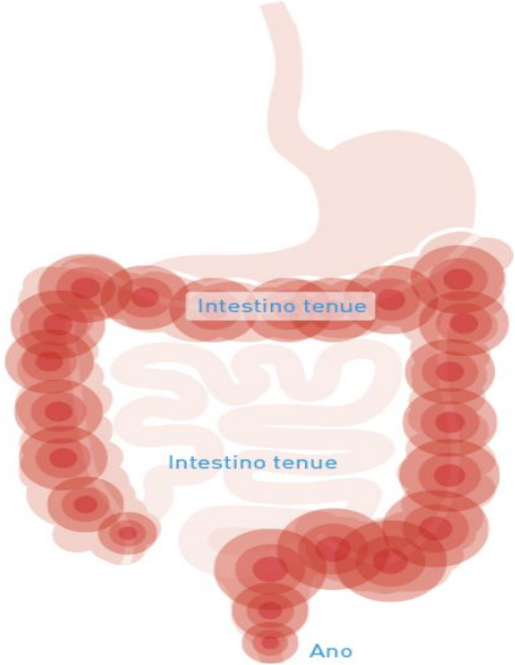
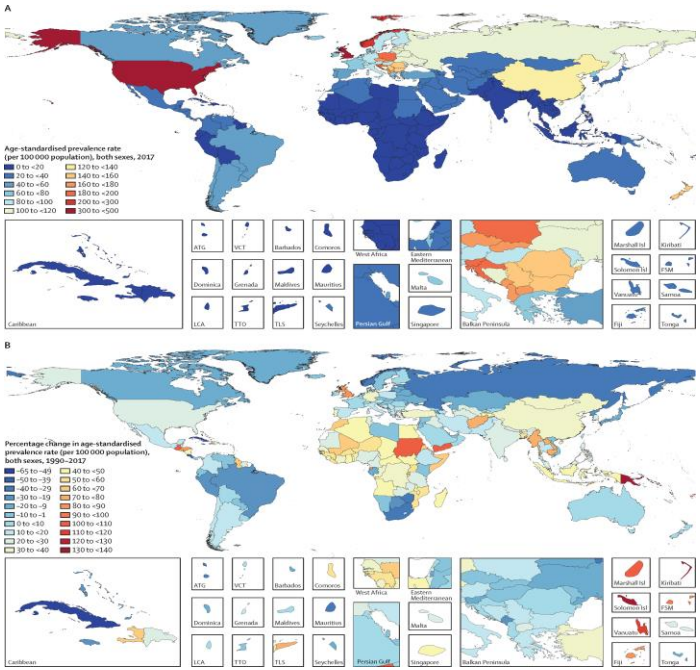
Crohn's Disease VS Ulcerative Colitis







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The Lancet Gastroenterology & Hepatology 2020 517-30DOI: (10.1016/S2468-1253(19)30333-4)

Table 1 Evolving incidence of IBD over the past generation throughout the world. The average annual percentage change (AAPC) reflects the percent change in incidence across the study periods: 95% confidence intervals (CI) that cross 0 are stable, below 0 are significantly decreasing, and above 0 are significantly increasing. Amalgamated data from Ng et al.'s systematic review, most recent study periods only [17••]

Country (region)	Time period	Average annual percent change (95% CI)	
		Crohn's disease	Ulcerative colitis
Canada (Manitoba) [18]	1990–2001	−0.4 (−2.4, 1.7)	−2.1 (−4.5, 0.5)
Canada (Ontario) [8]	1999–2008	1.7 (0.4, 2.9)	1.8 (0.5, 3.2)
Canada (Québec) [19]	2001–2008	−1.2 (−1.7, −0.7)	−3.6 (−5.3, −1.8)
Canada (Nova Scotia) [20]	1996–2009	−3.0 (−4.1, −1.9)	−1.2 (−2.4, −0.1)
Brazil (Piauí) [21]	1988–2012	11.1 (4.8, 17.8)	14.9 (10.4, 19.6)
Barbados (nationwide) [22]	2000–2004	−5.3 (−25.3, 20.1)	−2.6 (−21.5, 20.7)
China (Hong Kong) [23, 24]	1991–2006	4.4 (−0.7, 9.7)	1.8 (−10.0, 15.1)
Taiwan (nationwide) [25]	1998–2008	4.0 (1.0, 7.1)	4.8 (1.8, 8.0)
South Korea (Songpa) [26]	1991–2005	13.8 (8.7, 19.0)	9.5 (2.7, 16.7)
South Korea (nationwide) [27]	2006–2012	−2.4 (−4.7, 0.0)	−2.2 (−4.6, 0.2)
Malaysia (Kinta Valley) [28]	1990–2013	12.0 (−31.9, 84.0)	8.5 (1.8, 15.7)
Kuwait (nationwide) [29]	1990–1999	–	−1.7 (−8.9, 6.1)
Hungary (Veszprém) [30]	2002–2006	9.9 (−2.3, 23.6)	−6.2 (−20.2, 10.2)
Denmark (North Jutland) [31]	1988–2002	3.3 (−8.4, 16.6)	–
United Kingdom (Cardiff) [32]	2001–2005	1.1 (−0.8, 3.1)	–
Iceland (nationwide) [33]	1995–2009	−0.1 (−10.3, 11.3)	1.4 (−1.7, 4.6)
Sweden (Stockholm) [34]	1990–2001	2.2 (−2.2, 6.7)	–
Sweden (Uppsala) [35]	2005–2009	13.8 (2.4, 26.4)	5.3 (−1.5, 12.6)
Faroe Island (nationwide) [36]	2010–2014	2.3 (−9.5, 15.5)	2.0 (−15.8, 23.6)
Spain (Caceres) [37]	2000–2009	−3.8 (−18.7, 13.8)	2.4 (−10.0, 16.4)
Spain (Ciudad Real) [38]	2000–2012	7.2 (2.8, 11.8)	3.8 (−0.2, 7.9)
Croatia (Rijeka and Istria) [39]	1990–1994	7.8 (−1.4, 17.9)	–
Croatia (Zadar) [40]	2000–2010	13.5 (5.6, 21.9)	4.6 (−3.2, 13.1)
Croatia (Vukovarsko-Srijemska) [41]	1991–2010	4.5 (−0.3, 9.5)	12.3 (8.9, 15.8)
Malta (nationwide) [42]	1993–2005	0.8 (−6.5, 8.7)	4.6 (−0.8, 10.3)
Bosnia and Herzegovina (Tuzla) [43, 44]	1995–2006	34.4 (22.1, 47.9)	24.8 (11.0, 40.3)
France (Northern France) [45]	2006–2007	0.9 (−0.3, 2.2)	−1.3 (−2.8, 0.3)
Austria (Styria) [46]	1997–2007	2.7 (0.6, 4.8)	2.7 (0.0, 5.5)
Netherlands (South Limburg) [47]	1991–2002	−1.5 (−4.6, 1.6)	−5.4 (−8.1, −2.6)

Current Gastroenterology Reports (2019) 21: 40

IBD is stabilizing in the western countries and is accelerating in the westernized one.

TABLE 1 | Aminosalicylates.

Type of study	Patients	Treatment	Therapy period	Results/Conclusion	References
A review	UC patients	Oral 5-ASA	NA	5-ASA was more effective than placebo. There was no difference in clinical remission rates between once-daily dosing and conventional (twice or three times daily) dosing. Other 5-ASA formulations appeared to be as efficacious as SASP	(14)
A case-control study	UC patients	5-ASA	NA	Regular 5-ASA therapy reduced colorectal cancer risk by 75%	(15)
A meta-analysis	Patients with quiescent UC	5-ASA	6–24 months	Topical 5-ASA was effective in preventing relapse of UC in remission	(16)
A systematic review	CD patients	Oral 5-ASA	NA	No significant advantage was found in oral 5-ASA for the maintenance of medically-induced remission	(17)
A retrospective study	Adults with CD	5-ASA	NA	5-ASA was widely used as a long-term treatment for CD. The use of CD-related healthcare resources decreased significantly in the year following 5-ASA initiation	(18)
An updated cochrane review	CD patients in remission after surgery	Oral 5-ASA	NA	5-ASA drugs were superior to placebo for maintaining surgically-induced remission of CD. 5-ASA formulations appeared to be safe when compared with placebo, no treatment or biologics	(19)
A bayesian network meta-analysis	Mild-to-Moderate CD patients	Mesalamine, SASP, CSs, and budesonide	8–17 weeks	CSs and high-dose budesonide were effective treatments for inducing remission in mild-to-moderate CD. CSs were more effective than high-dose mesalamine, but high-dose mesalamine was an option among patients preferring to avoid steroids	(20)
A systematic review and meta-analysis	Adults with luminal CD in remission after a surgical resection	5-ASA	NA	5-ASA was of modest benefit in preventing relapse of quiescent CD after a surgical resection	(21)
A systematic review	Patients with mildly to moderately active CD	Aminosalicylates	NA	For induction therapy of mild to moderate CD, SASP had modest efficacy and high dose mesalamine (3–4.5 g/day) was not superior to placebo.	(22)

UC, ulcerative colitis; 5-ASA, 5-aminosalicylic acid; NA, not applicable; SASP, sulfasalazine; CD, Crohn's disease; CSs, corticosteroids.

TABLE 2 | Corticosteroids.

Type of study	Patients	Treatment	Results/Conclusion	Adverse events	References
A review	IBD patients	CSs and aminosalicylates	There were numerous adverse events of CSs, particularly at high doses and prolonged treatment. Therapy with budesonide may result in a better safety profile. 5-ASA treatment is usually well-tolerated, but with regard to the rare nephrotoxic events	CSs: opportunistic infections, diabetes mellitus, hypertension, ocular effects (glaucoma and cataracts), psychiatric complications, hypothalamic-pituitary-adrenal axis suppression and increased fracture risk	(29)
A systematic review	UC patients	Second-Generation oral CSs	Beclomethasone dipropionate and budesonide MMX have better efficacy in the induction of remission in UC than placebo or mesalazine. Second-generation CSs have a more favorable safety and tolerability than systemic CSs	Altered glucose concentration, constipation, menorrhagia, UC exacerbation, headache, nausea	(30)
A multi-center audit	IBD patients	CSs	14.9% of British patients with IBD experienced steroid dependency or excess	NA	(31)
A systematic review and meta-analysis	IBD patients	CSs	CSs were beneficial for inducing remission in UC, and might be effective in CD. Standard CSs were more effective than budesonide	NA	(33)
A prospective observational study	Adult outpatients with UC or CD	Oral prednisone (40 mg/day for 2 weeks, followed by a tapering course of 5 mg/day reduction every week)	CSs was associated with high rate of mood change in IBD patients when disease flares	Frequentmood changes	(34)
A systematic review and meta-analysis	IBD patients with CMV	CSs, TPs, TNF antagonists	Exposure to CSs or TPs, but not anti-TNF drugs, was associated with an increased risk of CMV reactivation in IBD patients	CMV reactivation	(35)
A retrospective review	IBD patients	CSs	Prolonged use of CSs was associated with significant harm to IBD patients	VTE, fragility fracture, infections	(36)
A retrospective survey	UC patients	Oral or intravenous CSs	The majority of UC patients primarily responded to CSs. But after 1 year of treatment, nearly half of patients were assessed as CS dependence	NA	(37)
A retrospective study	Adults with IBD	CSs	The use of CSs significantly increased the risk of VTE	VTE	(38)
A population-based cohort study with a nested case-control analysis	Incident IBD patients aged ≥66 years	Systemic oral CSs	Oral CSs were associated the increase risk of serious infections in elderly-onset IBD patients	Diabetes, chronic respiratory diseases, chronic kidney diseases, cancer	(39)
A retrospective cohort study	UC patients	CSs	About half of newly-diagnosed patients with UC required CSs. Among CS users, one third of the patients had a sustained response after the initial CSs course while two-thirds required further CSs therapy	NA	(40)
Two randomized, double-blind, placebo-controlled, phase 3 studies	Patients with mild-to-moderate active UC	Budesonide MMX (9 or 6 mg once daily)	Budesonide MMX 9 mg resulted in significantly higher combined clinical and colonoscopic remission rates ($P = 0.0002$)	Headache, nausea, abdominal pain, nasopharyngitis	(41)
A phase III, randomized, double-blind, double-dummy, placebo-controlled, parallel-group trial	Patients with active, mild-to-moderate UC	Budesonide MMX (9 mg/day)	Budesonide MMX 9 mg appeared to be safe and more effective than placebo at inducing combined clinical and endoscopic remission in patients with active, mild-to-moderate UC	Headache, flatulence, nausea, blood cortisol decrease	(42)

IBD, inflammatory bowel disease; CSs, corticosteroids; 5-ASA, 5-aminosalicylic acid; UC, ulcerative colitis; MMX, Multi Matrix; NA, not applicable; CD, Crohn's disease; CMV, cytomegalovirus; TNF, tumor necrosis factor; VTE, venous thromboembolism.

TABLE 3 | Small molecules.

Type of study	Patients	Treatment	Median treatment duration	Median follow-up duration	Results/Conclusion	Adverse events	References
Three phase 3, randomized, double-blind, placebo-controlled trials	Adults with UC	Tofacitinib (induction therapy:10 mg twice daily for 8 weeks; maintenance therapy: either 5 or 10 mg twice daily for 52 weeks)	8, 8, 52 weeks	8, 8, 52 weeks	Tofacitinib appeared more effective in inducing and maintaining remission in patients with active CD compared with placebo	Increased lipid levels, infections, cardiovascular events	(105)
A phase 2, double-blind, randomized, placebo-controlled trial	Patients with moderate-to-severe CD	Filgotinib (GLPG0634, GS-6034) (200 mg once daily)	10 weeks	20 weeks	Filgotinib was more effective for inducing remission than placebo, and it had an acceptable safety profile	Infections	(106)
A multicenter, double-blind, phase 2b study	Adults with moderately to severely active UC and an inadequate response, loss of response, or intolerance to CSs, immunosuppressors, and/or biologics	Upadacitinib (7.5, 15, 30, or 45 mg once daily)	8 weeks	8 weeks	Upadacitinib (45 mg) was more efficacious as induction therapy than placebo	Increased serum lipid levels and creatine phosphokinase, herpes zoster, pulmonary embolism, deep venous thrombosis	(107)
A double-blind, placebo-controlled phase 2 trial	Adults with moderate-to-severe UC	Ozanimod (RPC1063) (0.5 or 1 mg daily)	32 weeks	32 weeks	Ozanimod at a daily dose of 1 mg resulted in a slightly higher rate of clinical remission of UC than placebo	Pyrexia, arthralgia, alanine aminotransferase increased, rash, vomiting, orthostatic hypotension, aspartate aminotransferase increased, hyperbilirubinemia, insomnia, nasopharyngitis, proctalgia	(108)
A phase 3, multicenter, randomized, double-blind, placebo-controlled trial	Patients with moderately to severely active	Oral ozanimod hydrochlorid (1 mg once daily) for induction therapy	10, 10, 52 weeks	10, 10, 52 weeks	Ozanimod resulted in significantly increased incidences of clinical response and clinical remission for both induction and maintenance period	Elevated liver aminotransferase levels, nasopharyngitis, headache, arthralgia	(109)
A single-arm, phase 2, prospective observer-blinded endpoint study	Adults with moderately to severely active CD	Ozanimod (0.25 mg daily for 4 days, followed by 3 days at 0.5 mg daily, then 1.0 mg daily for a further 11 weeks, followed by a 100-week extension)	12 weeks	112 weeks	Endoscopic, histological, and clinical improvements were seen within 12 weeks of initiating ozanimod therapy in patients with moderately to severely active CD	CD(flare), abdominal pain, lymphopenia, arthralgia, nausea	(110)
A phase 2, proof of concept, double-blind, parallel-group study	Patients with moderately to severely active UC	Etrasimod (APD334) (1 or 2 mg once daily)	12 weeks	12 weeks	Erasimod 2 mg was more effective than placebo in producing clinical and endoscopic improvements	Anemia, urinary tract infection, headache, blood creatine phosphokinase increased, gamma-glutamyltransferase increased, sinusitis, fever, hyperlipasemia	(111)

UC, ulcerative colitis; CD, Crohn's disease; CSs, corticosteroids.

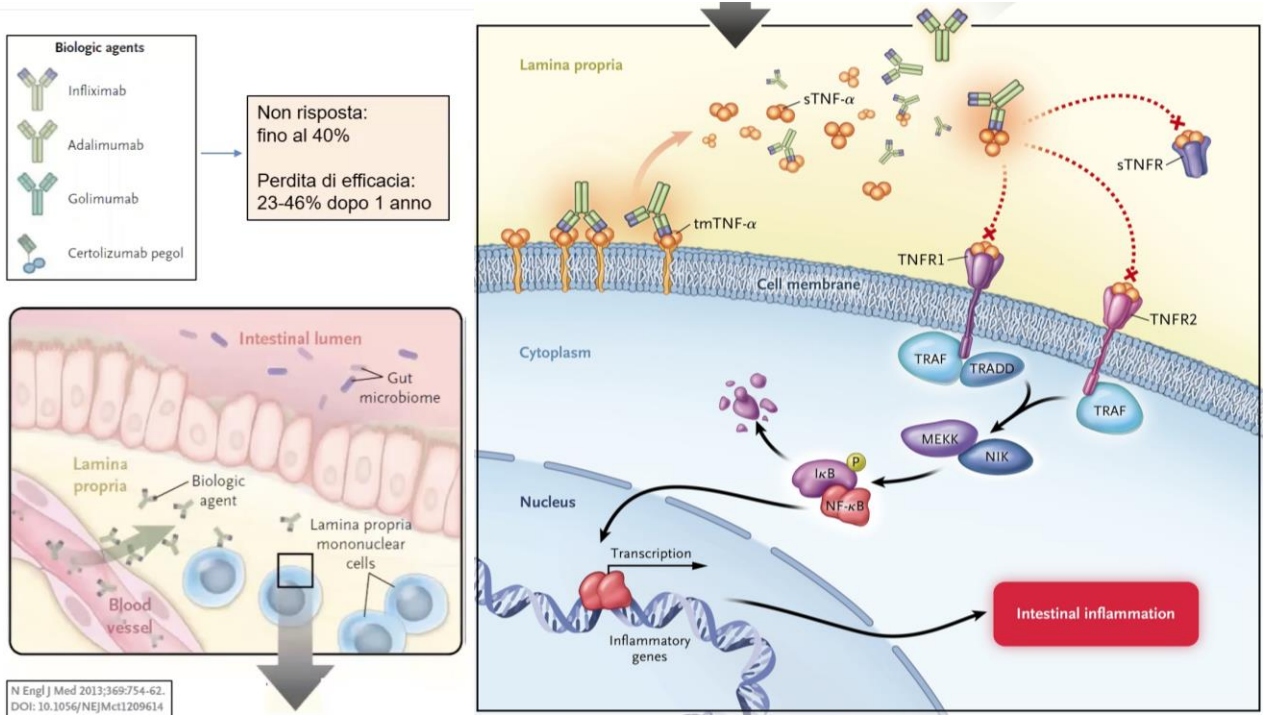
Immunomodulators

Immunomodulators are important for patients with IBD and mainly include thiopurines (TPs), methotrexate (MTX), calcineurin inhibitors, and Janus Kinase (JAK) inhibitors. The studies on the efficacy and safety of immunomodulators in IBD are summarized in **Supplementary Table 1**.

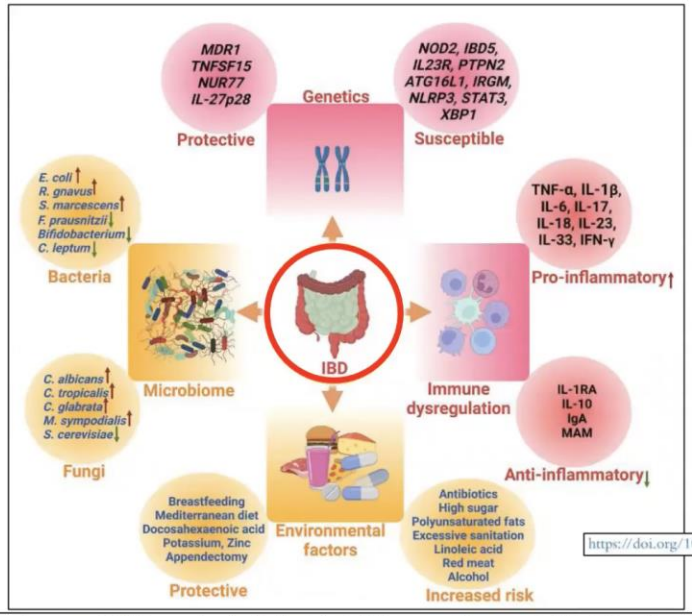
Biologics

Biologics mainly include pro-inflammatory cytokine inhibitors and integrin antagonists. The pro-inflammatory cytokines, TNF-α and IL-12/23, play an important role in the pathogenesis of IBD. Studies on the efficacy and safety of biologics in IBD treatment are summarized in **Supplementary Table 2**.

Front. Med. 8:765474.
doi: 10.3389/fmed.2021.765474



N Engl J Med 2013;369:754-62.
DOI: 10.1056/NEJMct1209614



https://doi.org/10.1016/bs.pmbts.2022.09.003

The exact cause of IBD remains indistinct, but it is generally accepted that its etiopathology is multifactorial, involving genetic predisposition, mucosal barrier dysfunction, disturbances in the gastrointestinal microbiota, dysregulated immune responses, environmental, and lifestyle factors

Why microbiota and IBD?

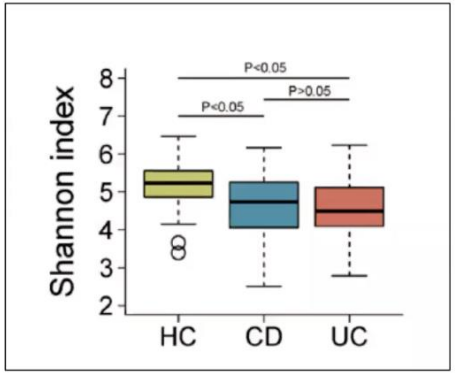
Gut microbiota composition is altered in IBD vs controls

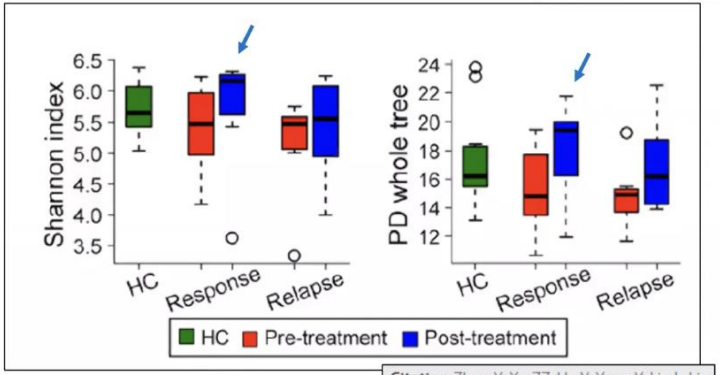
Gut microbiota composition is altered in active vs non-active IBD

Gut microbiota can influence the development of IBD

Association → **Causal relationship**

Stool gut α-biodiversity in IBD

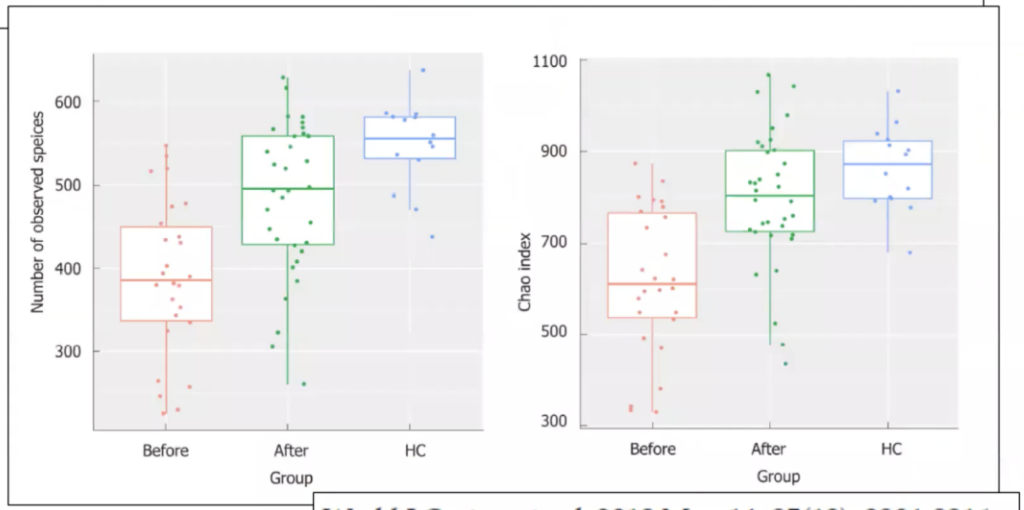




Citation Zhou Y, Xu ZZ, He Y, Yang Y, Liu L, Lin Q, Nie Y, Li M, Zhi F, Liu S, Amir A, González A, Tripathi A, Chen M, Wu GD, Knight R, Zhou H, Chen Y. 2018. Gut microbiota offers universal biomarkers across ethnicity in inflammatory bowel disease diagnosis and infliximab response prediction. mSystems 3:e00188-17. https://doi.org/10.1128/mSystems.00188-17.

Mucosal gut α-biodiversity in IBD

Figure 1 Richness and diversity in the mucosa-associated microbiota of the patients with Crohn's disease and healthy controls before and after induction of remission.



World J Gastroenterol 2019 May 14; 25(18): 2204-2216

Microbiota alpha diversity

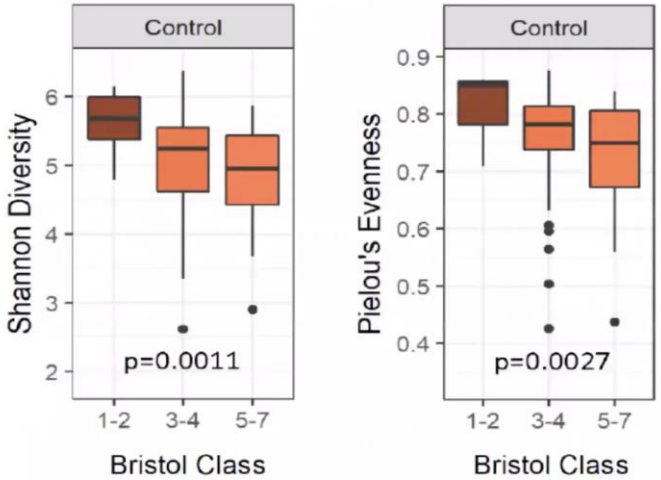
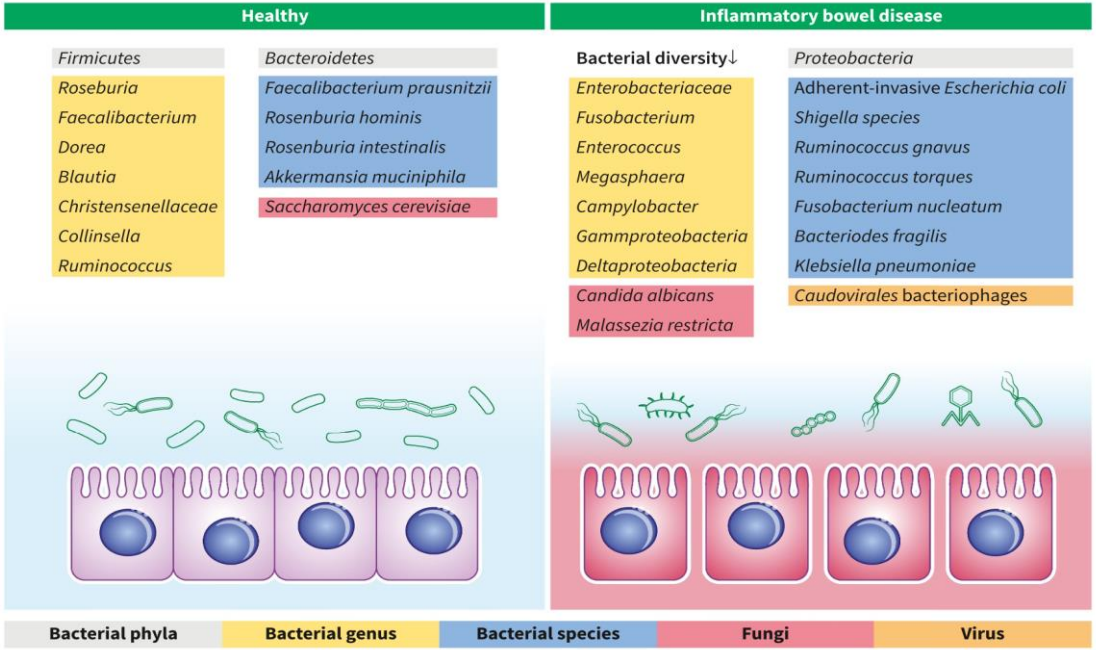


Table 1 Bacterial and fungal dysbiosis in the gastrointestinal tract of IBD patients.

Name of the microbes	Relative abundance in IBD	Important molecules/functions	Reference
Faecalibacterium prausnitzii	Decreased	Short-chain fatty acids, Microbial anti-inflammatory molecule	17
Prevotella copri	Decreased	Butyrate and propionate	17
Ruminococcus, Roseburia, Coprococcus, Blautia, Eubacterium and *Dorea*	Decreased	Short-chain fatty acids	17
Bifidobacterium adolescentis	Decreased	Tryptophan production	18
Ruminococcus gnavus	Increased	Production of mucolytic enzymes	19
Alistipes massiliensis	Increased	Inflammation	17
Alistipes putredinis	Increased	Hydrolyze tryptophan to Indole	20
Escherichia coli	Increased	Lipopolysaccharides	18
Serratia marcescens	Increased	Lipopolysaccharides	19
Bacteroides fragilis	Increased	Polysaccharide A	21
Bacteroides vulgatus	Increased	Succinate	22
Streptococcus anginosus	Increased	Group G antigens	23
Aggregatibacter segnis	Increased	Short-chain fatty acids	24
Clostridium difficile	Increased	Exotoxins (toxin A and toxin B)	25
Helicobacter hepaticus	Increased	Through recruitment of neutrophils	26
Klebsiella pneumoniae	Increased	Haemolysin co-regulated protein	27
Candida albicans	Increased	Candidalysin	
Candida tropicalis	Increased	Associated with anti-*S. cerevisiae* antibodies	

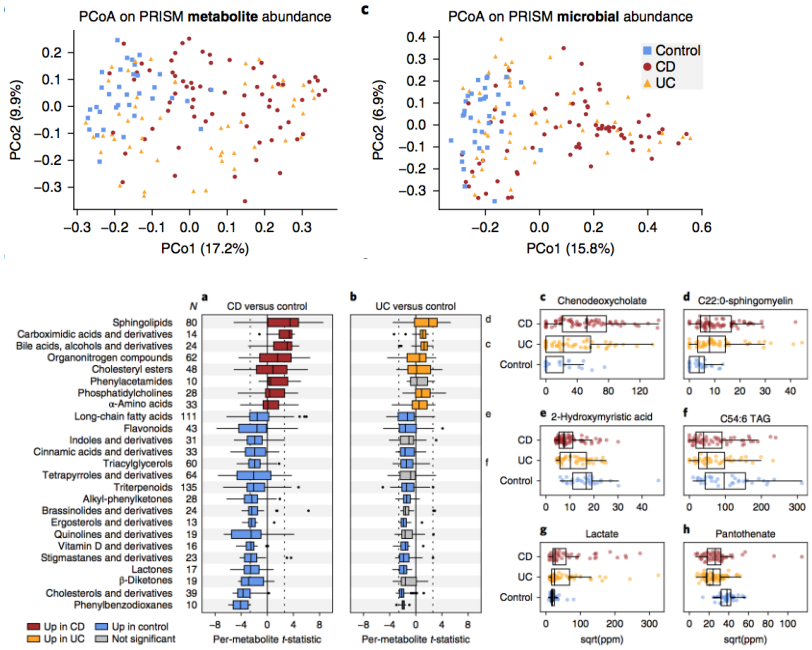
https://doi.org/10.1016/bs.pmbts.2022.09.003

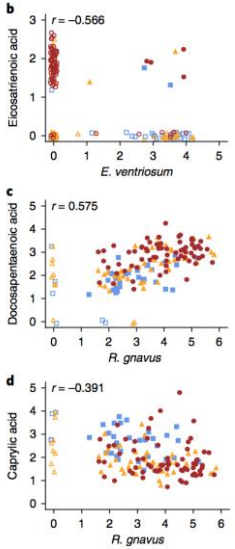
Microbial alterations in IBD



Zheng et al, UEGJ 2022

Metabolomic alterations in IBD

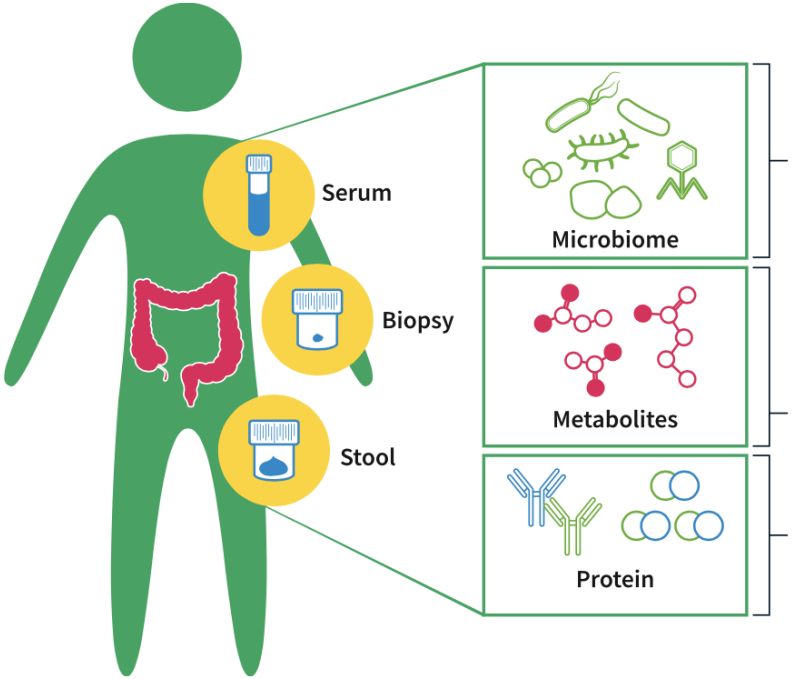




Short-chain fatty acids
Medium-chain fatty acids
Tryptophan
Bile acids
Sphingolipids

Franzosa et al, Nature 2019

Metaproteomic alterations in IBD



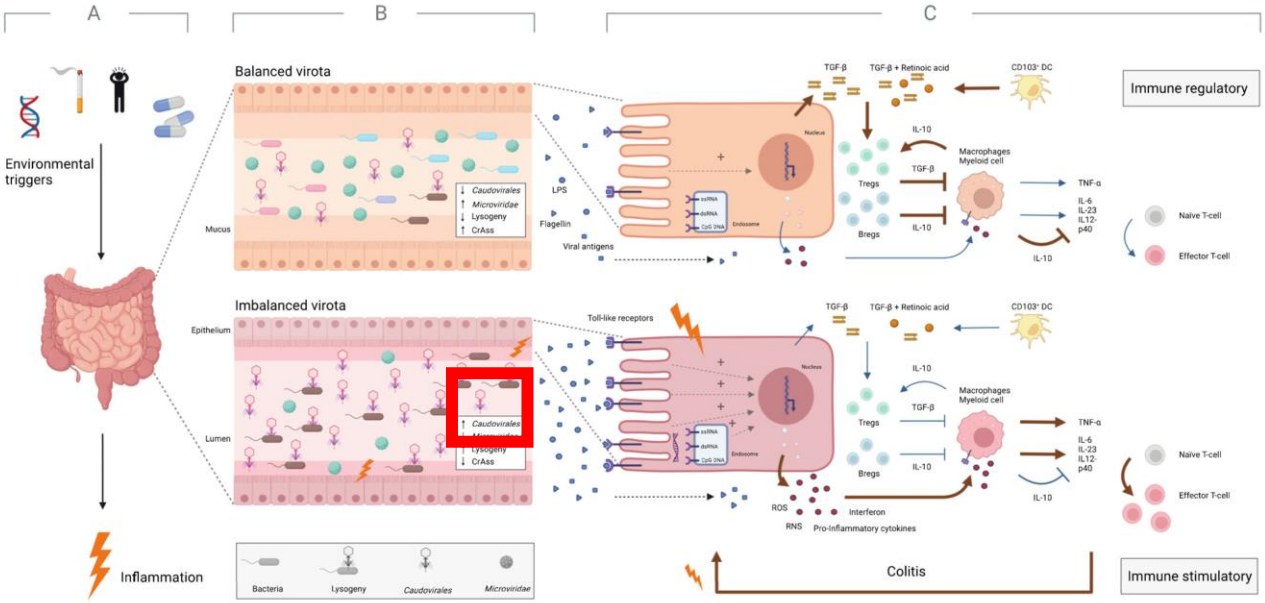
- *Faecalibacterium prausnitzii*
- *Faecalibacterium* genus
- *Peptostreptococcaceae* genus
- *Anaerostipes* genus
- *Methanobrevibacter* genus
- *Christensenellaceae* genus
- *Collinsella* genus
- *Escherichia* genus
- Microbial dysbiosis index
- Microbial load

- Short chain fatty acids (butyrate, acetate)
- Bile acid derivatives
- Tryptophan metabolities
- Sphingolipids

- Matrix metalloproteinase - 9
- Matrix metalloproteinase - 14
- Tissue inhibitor of metalloproteinase 1

Zheng et al, UEGJ 2022

IBD patients possess an imbalanced intestinal Virome and a dysregulated immune system



Jansen D, et al. Viruses. 2023

I butirrato-produttori

Produttori principali

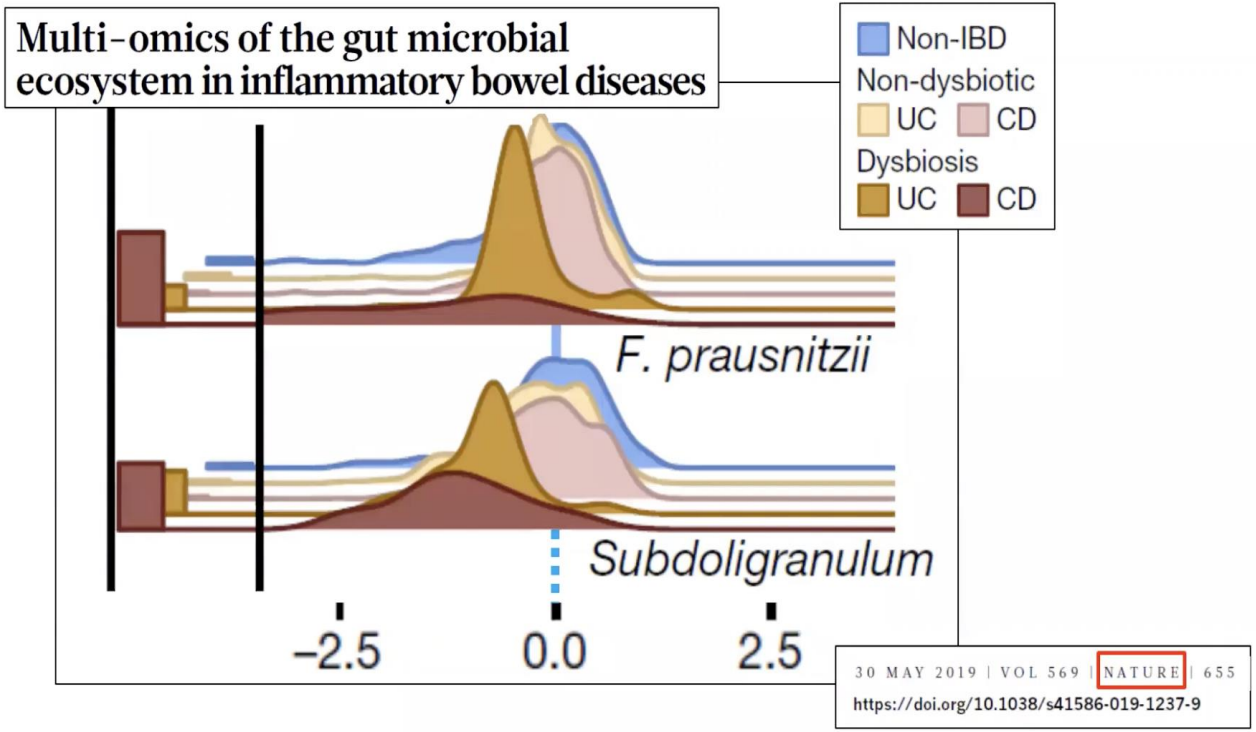
Faecalibacterium (6-7%)
Roseburia (2%)
Agathobacter (2%)

I primi due sono riforniti da acetogeni, l'ultimo da *Ruminococcus* (*R. bromii* e/o *R. obei*) che funge da primo fermentatore.

Produttori minori

Coprococcus
Subdoligranulum
Butyricicoccus
Butyrivibrio
Holdemanella
C. butyricum

Eubiotici, protettori verso IBD, adenomi, CCR, depressione.
In eccesso: meteorismo, tendenza al sovrappeso.



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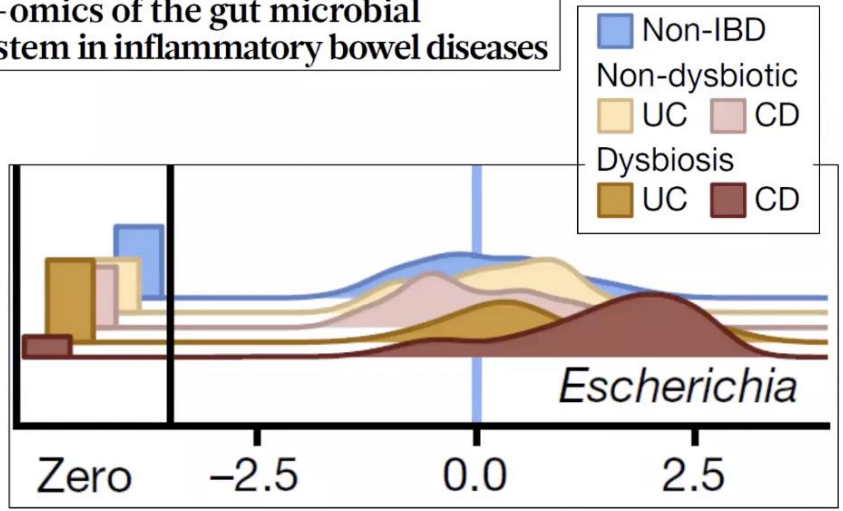
https://doi.org/10.1038/s41586-019-1237-9

Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases



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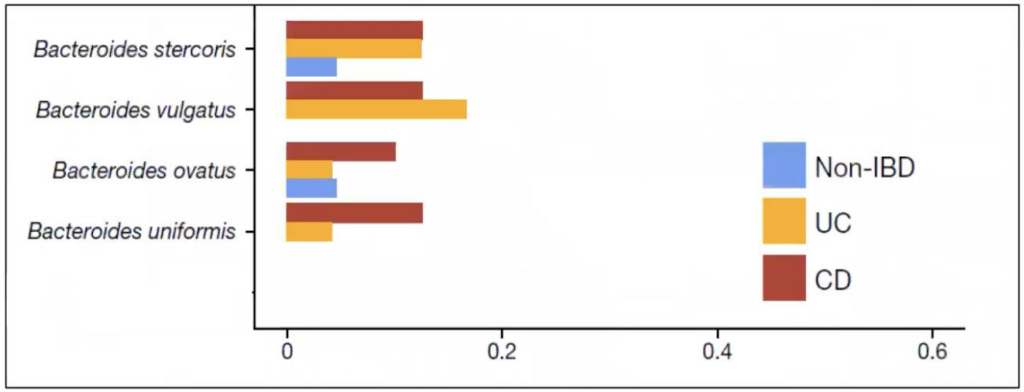

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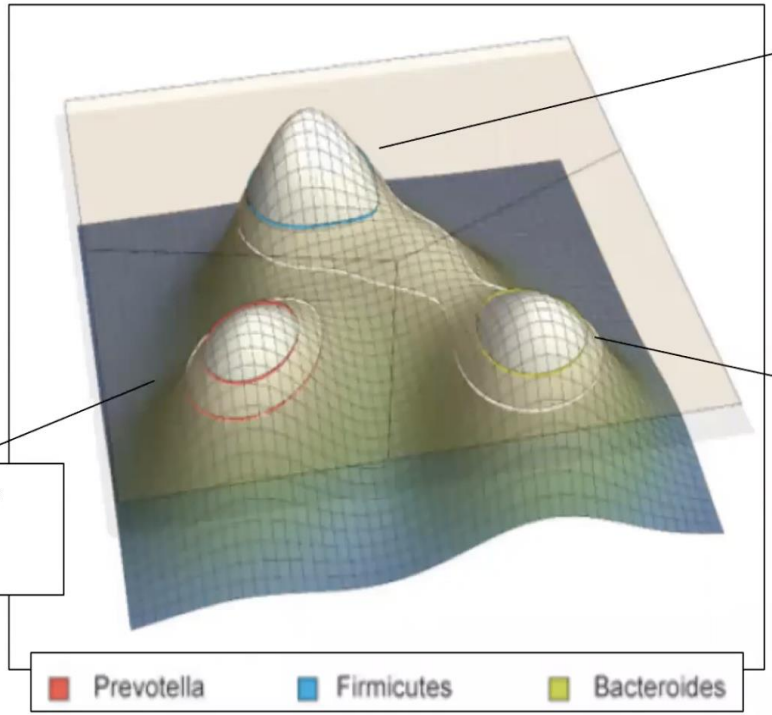


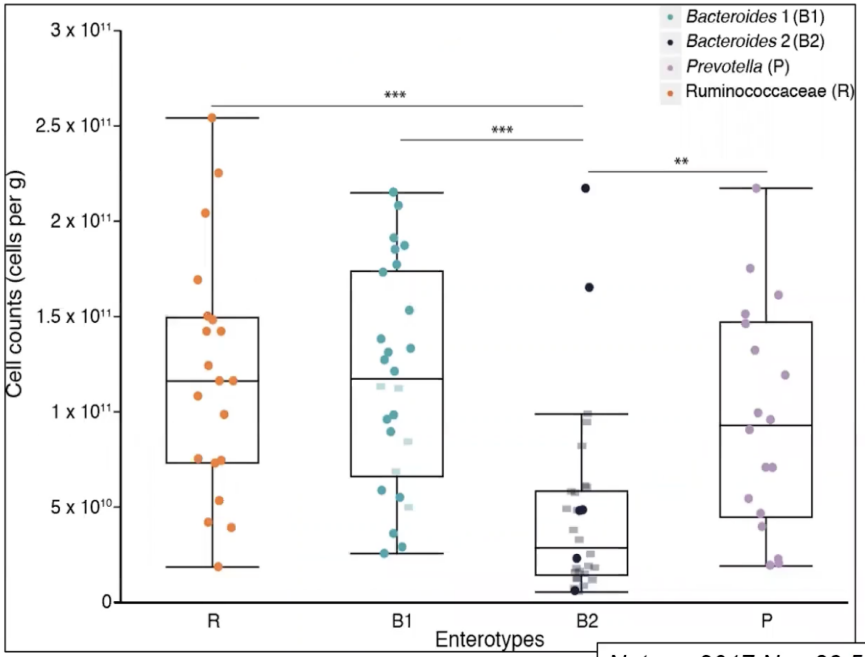
Malattie cardio-vascolari
Malattie neurologiche

NASH
Sindrome metabolica
PCOS
CCR
IBD
Celiachia
Immuno-senescenza
Depressione

Artrite reumatoide
HIV
Ipertensione

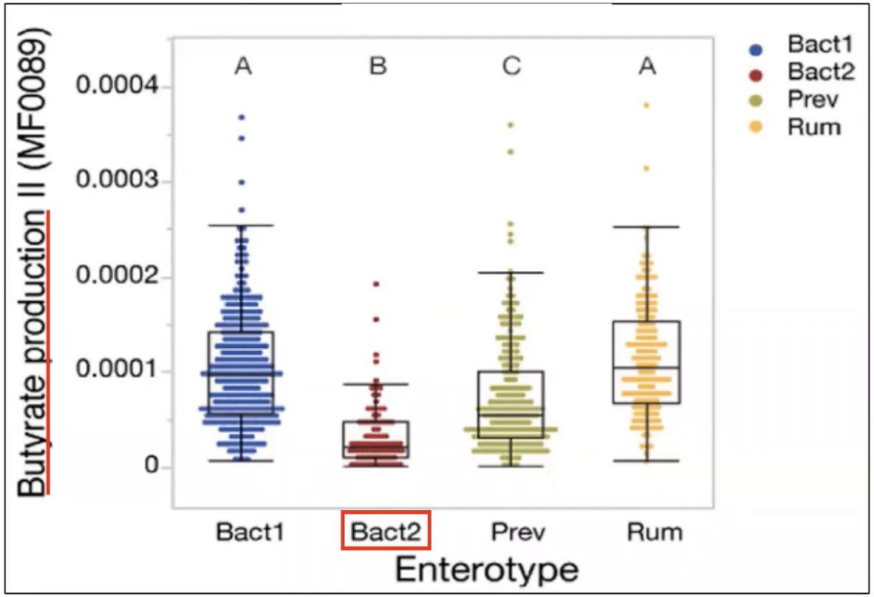
Nat Microbiol. 2018 January ; 3(1): 8–16.

Faecal microbial loads vary across enterotypes.



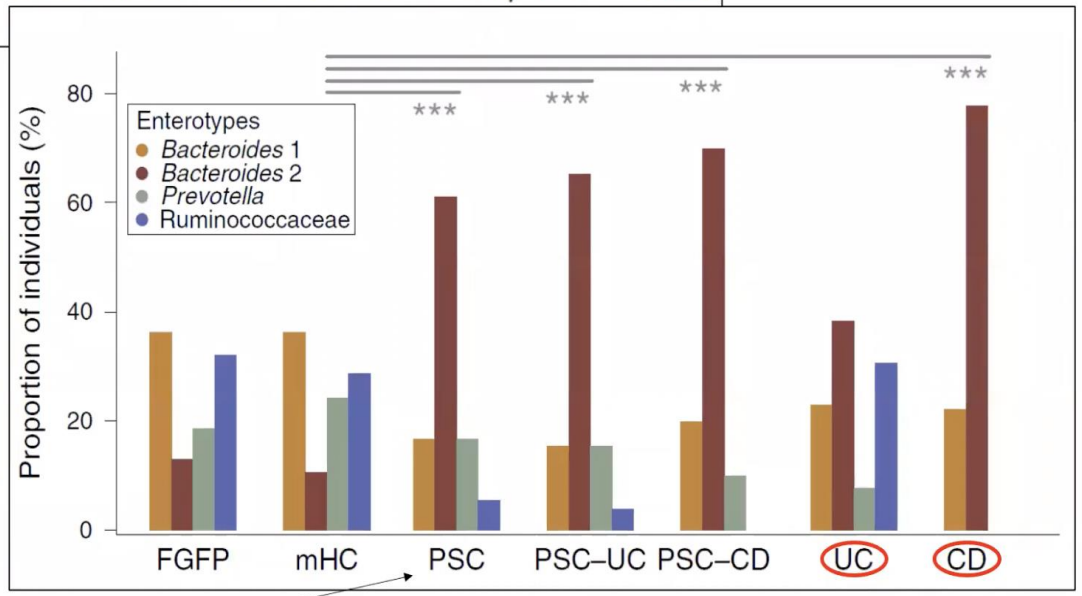
La *bacterial load*
(per grammo di feci coloniche)
tra B1 e B2,
può variare anche di 10 volte!

Nature. 2017 Nov 23;551(7681):507-511



Nature | Vol 581 | 21 May 2020

We showed how stool moisture, faecal calprotectin levels and CRP concentrations were closely associated with faecal cell counts and the recently described B2 enterotype.



La colangite sclerosante primitiva provoca infiammazione, fibrosi e stenosi dei dotti biliari, senza che sia nota la causa.
Tuttavia, l'80% dei pazienti è anche affetto da una malattia infiammatoria intestinale cronica, il più delle volte CU.

primary sclerosing cholangitis (PSC)

NATURE MICROBIOLOGY | VOL 4 | NOVEMBER 2019 | 1826–1831 |

> Am J Gastroenterol. 2010 Nov;105(11):2420-8. doi: 10.1038/ajg.2010.281. Epub 2010 Jul 20.

Mucolytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria

Chin Wen Png [1], Sara K Lindén, Kristen S Gilshenan, Erwin G Zoetendal, Chris S McSweeney, Lindsay I Sly, Michael A McGuckin, Timothy H J Florin

Affiliations + expand

PMID: 20648002 DOI: 10.1038/ajg.2010.281

Abstract

Objectives: Mucosa-associated bacteria are increased in inflammatory bowel disease (IBD), which suggests the possibility of an increased source of digestible endogenous mucus substrate. We hypothesized that mucolytic bacteria are increased in IBD, providing increased substrate to sustain nonmucolytic mucosa-associated bacteria.

Methods: Mucolytic bacteria were characterized by the ability to degrade human secretory mucin (MUC2) in pure and mixed anaerobic cultures. Real-time PCR was used to enumerate mucosa-associated mucolytic bacteria in 46 IBD and 20 control patients. Bacterial mucolytic activity was tested in vitro using purified human MUC2.

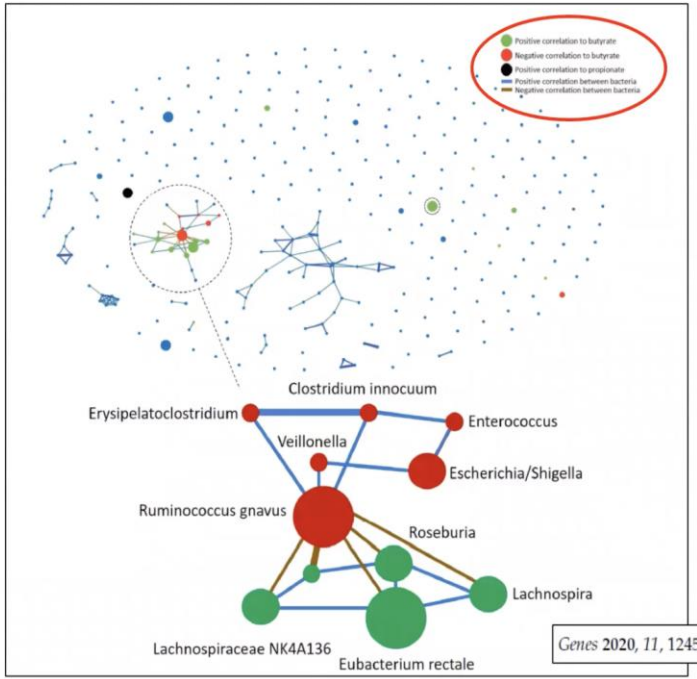
Results: We confirm increased total mucosa-associated bacteria 16S rRNA gene in macroscopically and histologically normal intestinal epithelium of both Crohn's disease (CD) (mean 1.9-fold) and ulcerative colitis (UC) (mean 1.3-fold). We found a disproportionate increase in some mucolytic bacteria. Mean Ruminococcus gnavus were increased >4-fold and Ruminococcus torques ~100-fold in macroscopically and histologically normal intestinal epithelium of both CD and UC. The most abundantly detected mucolytic bacterium in controls, Akkermansia muciniphila, was reduced many fold in CD and in UC. Coculture of A. muciniphila with MUC2 as the sole carbon source led to reduction in its abundance while it augmented growth of other bacteria.

Conclusions: Mucolytic bacteria are present in healthy humans, where they are an integral part of the mucosa-associated bacterial consortium. The disproportionate increase in R. gnavus and R. torques could explain increased total mucosa-associated bacteria in IBD.

Study	Subject	Samples	Method	Major findings	Country
Mucosa-associated microbiota in IBD patients					
Walker AW, 2011 [12]	CD ($n = 12$), UC ($n = 12$), C ($n = 6$)	Mucosal biopsies of inflamed and non-inflamed tissue	Sequencing of nearly full-length 16S rRNA ($n = 10.000$) qPCR	Mucosal-microbial diversity is reduced (predominantly CD) Significant difference between inflamed and non-inflamed ↓ Firmicutes ↑ Bacteroides ↑Enterobacteriaceae (only CD)	UK
Png CW, 2010 [1]	CD ($n = 26$), UC ($n = 2$), C ($n = 20$)	Mucosal biopsies of inflamed and non-inflamed tissue	RT-PCR	Total bacteria were increased in non-inflamed biopsies of IBD patients Mucolytic bacteria are increased in IBD patients ↓ *Akkermansia muciniphila* in IBD patients ↑ *R. gnavus* and *R. torques*	Australia
Swidsinski A, 2005 [107]	IBD ($n = 20$), IBS ($n = 20$), C ($n = 20$)	Mucosal biopsy	FISH	Biofilm formation of *B. fragilis* in IBD patients Density of the biofilm is increased in IBD patients	Germany
Willing BP, 2010 [11]	Concordant and disconcordant twin pairs ($n = 9$)	Mucosal samples	454-Pyrosequencing	Similar microbial composition throughout the colon in IBD patients ↑ *R. gnavus* in CD patients	Sweden
Frank DN, 2007 [104]	CD, UC, C (total $n = 190$)	Resected tissues	Sequencing of nearly full-length 16S rRNA ($n = 15.172$) qPCR	↓ Bacteroidales and Lachnospraceae ↑ Alpha, Beta and Gammaproteobacteria, Actinobacteria	USA

Best Practice & Research Clinical Gastroenterology 27 (2013) 25–38

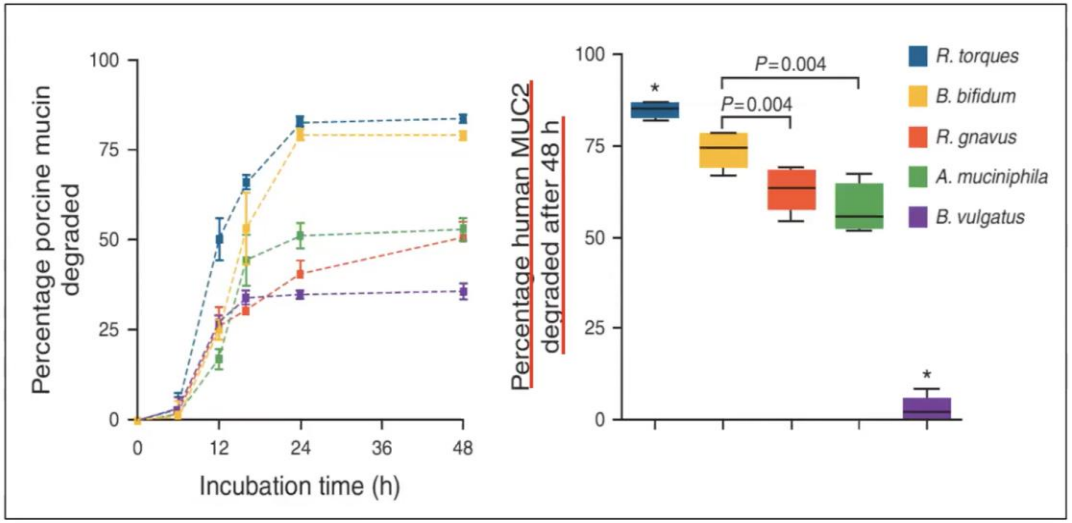
Covariance Systems



Genes **2020**, *11*, 1245; doi:10.3390/genes11111245

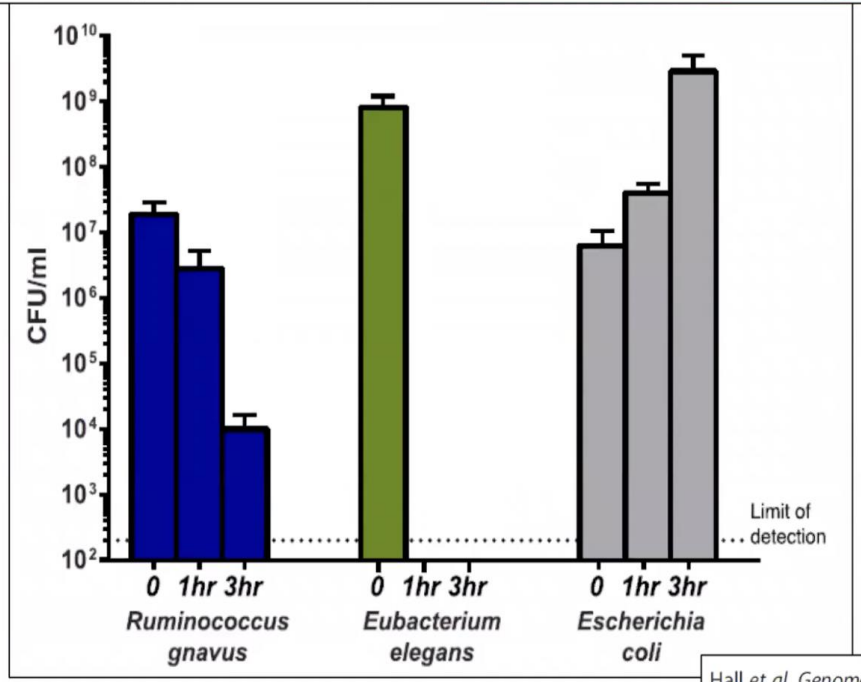
Harmful is to be firmicutes, because the F. work at low pH

Previously identified mucolytic bacteria, with the exception of *B. vulgatus*, degrade human MUC2 *in vitro*



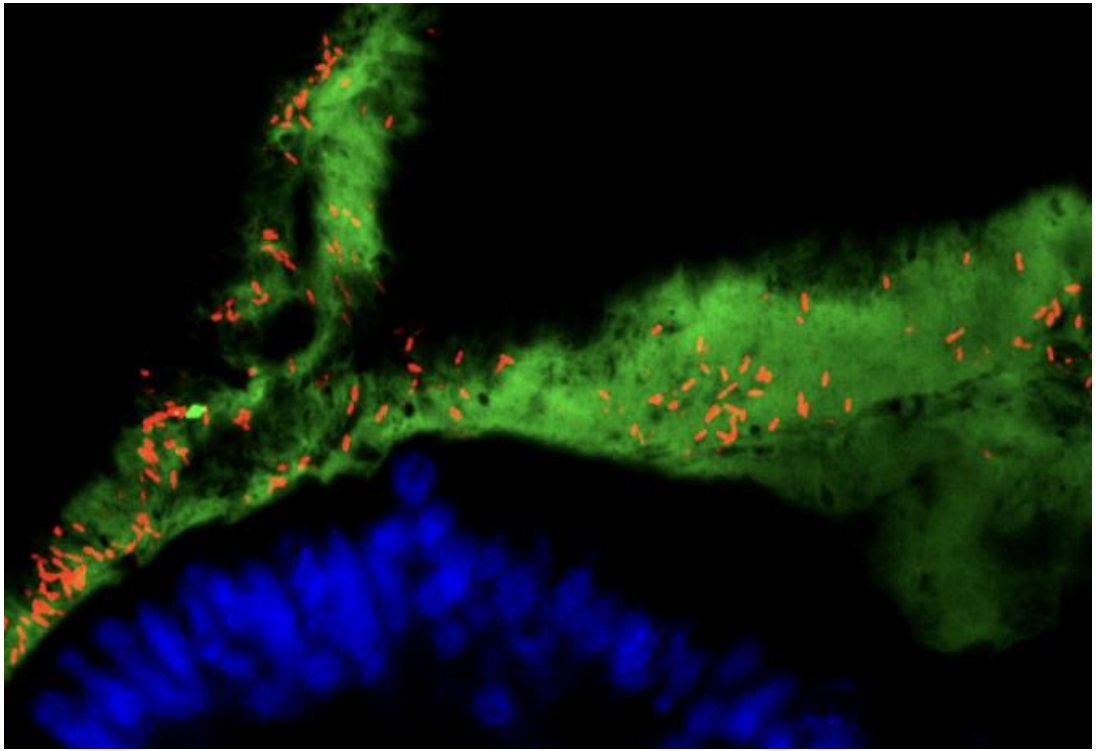
Am J Gastroenterol advance online publication, 20 July 2010; doi:10.1038/ajg.2010.281

R. gnavus, *Eubacterium elegans*, and *E. coli* at 0, 1, and 3 h post-transfer to atmospheric oxygen conditions



Hall *et al. Genome Medicine* (2017) 9:103
DOI 10.1186/s13073-017-0490-5

What turns on the R. Gnavus e Torques? Not eating or eating little fiber means not nourishing the microbiota and imposing the 'increase of the mucus-eating bacteria, so under pathological conditions, the selection of R.Gnavus and R. Torques is turned on, which by resisting O2 perforate the enteric mucosa



B. thetaiotaomicron, commensale non patogeno…

↓

È un Bacteroides: esige un pH vicino alla neutralità

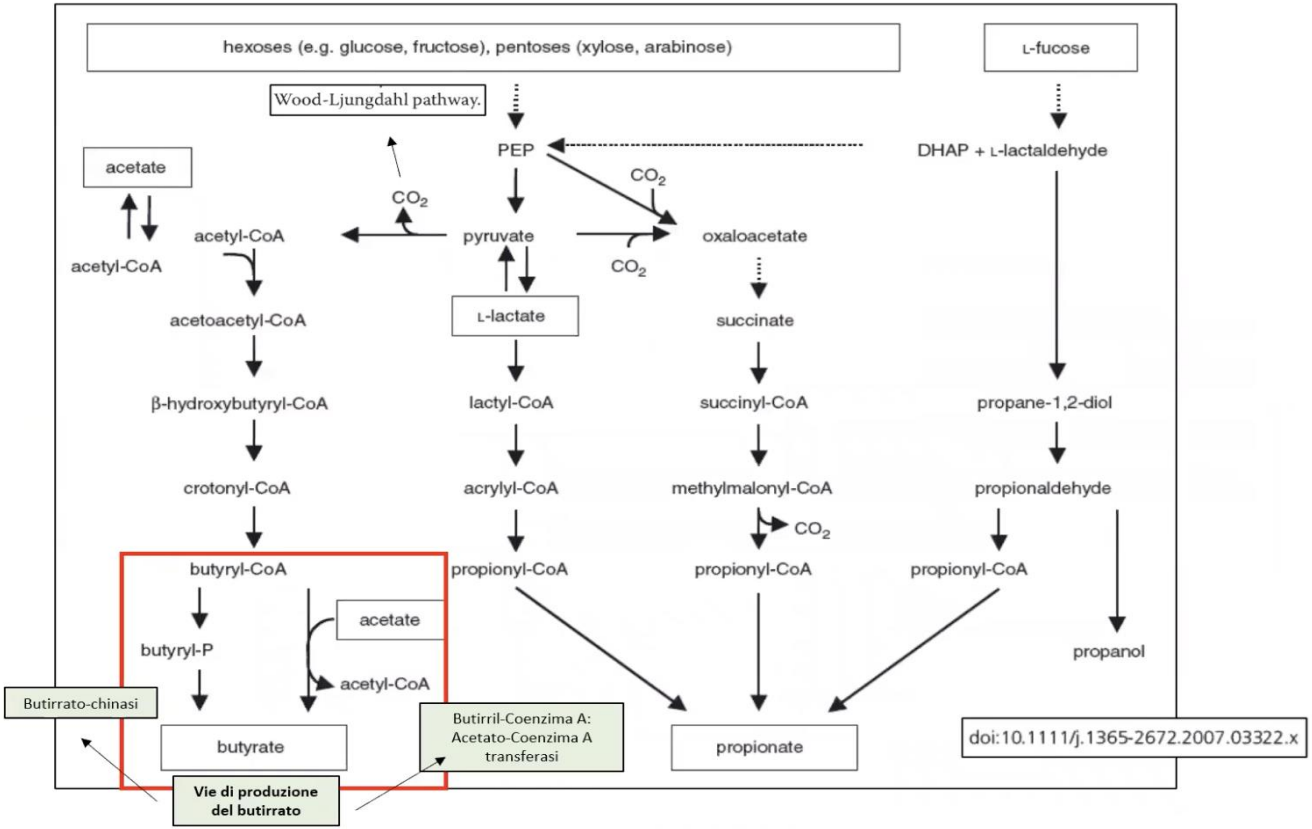
R. gnavus e R. torques sono Firmicutes e quindi operano a pH sia acido che neutro

↓

Ma a pH neutro è più performante Bacteroides

↓

In condizioni di patologia il pH è più acido e questo favorisce R. gnavus e R. torques.


hexoses (e.g. glucose, fructose), pentoses (xylose, arabinose)
L-fucose
Wood-Ljungdahl pathway.
PEP
DHAP + L-lactaldehyde
acetate
CO_2
CO_2
acetyl-CoA
pyruvate
oxaloacetate
acetyl-CoA
CO_2
acetoacetyl-CoA
L-lactate
succinate
β-hydroxybutyryl-CoA
lactyl-CoA
succinyl-CoA
propane-1,2-diol
crotonyl-CoA
acrylyl-CoA
methylmalonyl-CoA
propionaldehyde
CO_2
butyryl-CoA
propionyl-CoA
propionyl-CoA
propionyl-CoA
acetate
butyryl-P
propanol
acetyl-CoA
Butirrato-chinasi
Butirril-Coenzima A: Acetato-Coenzima A transferasi
butyrate
propionate
doi:10.1111/j.1365-2672.2007.03322.x
Vie di produzione del butirrato

Ex novo

Butyrate is generally formed by condensation of two molecules of acetyl-CoA via either butyrate kinase or butyryl-CoA:acetate CoA-transferase. Study of the human gut microbiota via primers for the genes encoding these enzymes showed that in most cases butyryl-CoA:acetate CoA-transferase, rather than butyrate kinase, appears to perform the final step in butyrate synthesis and is possible only in the presence of acetate (Louis *et al.*, 2004). Butyrate production is widely distributed among phylogenetically diverse human colonic Gram-positive *Firmicutes*. Two abundant groups are related to *Eubacterium rectale/ Roseburia* spp. and to *Faecalibacterium prausnitzii* (Louis *et al.*, 2010). While most species have the capacity for either propionate or butyrate production from hexose sugars, some species of *Lachnospiraceae* (*C. catus* and *R. inulinivorans*) have been demonstrated to switch from butyrate to propionate production on different substrates (Reichardt *et al.*, 2014; Scott *et al.*, 2006). Besides these pathways for SCFA production, there will be numerous other routes to SCFA as some microbes grow on intermediate products of fermentation, such as hydrogen gas (H_2), lactate, succinate, formate and ethanol, and convert these to end products including SCFA. Other microbes, particularly Archaea species can metabolise carbon dioxide (CO_2) either yielding methane (CH_4) or acetate.

Beneficial Microbes, 2020; 11(5): 411-455

Butirrato chinasi:
Coprococcus eutactus
Coprococcus comes
Clostridium butyricum

Ex novo

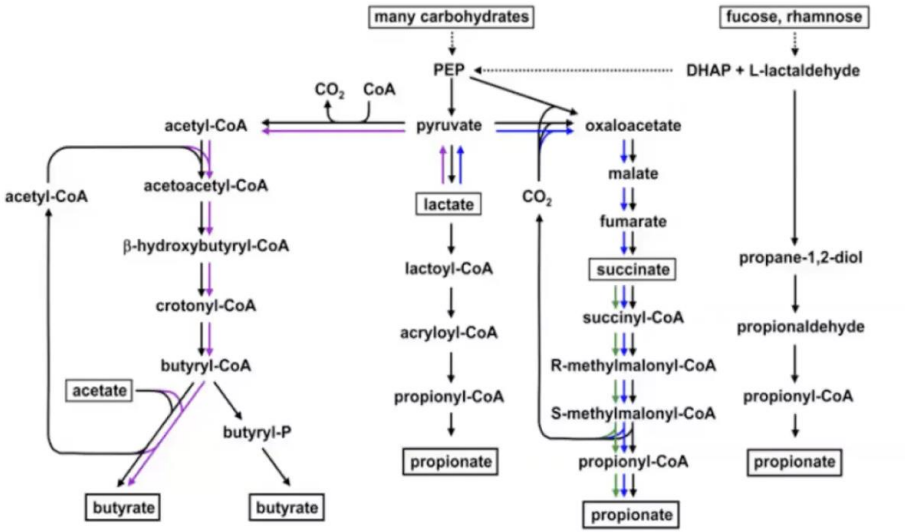
Butirril-Coenzima A: Acetato-Coenzima A transferasi:
Agathobacter rectale
***Roseburia* spp.**
Faecalibacterium prausnitzii
Coprococcus catus

Dimerizzando l'acetato

Butirril-Coenzima A: Acetato-Coenzima A transferasi:
***Anaerostipes* spp.**
Eubacterium hallii
L'acetil-Coenzima A utilizzato da questi batteri deriva dal lattato (via dell'acrilato)

Dal lattato

H. J. Flint *et al.*



Proceedings of the Nutrition Society (2015), **74**, 13–22

Butyrate is generally formed by condensation of two molecules of acetyl-CoA via either butyrate kinase or butyryl-CoA:acetate CoA-transferase. Study of the human gut microbiota via primers for the genes encoding these enzymes showed that in most cases butyryl-CoA:acetate CoA-transferase, rather than butyrate kinase, appears to perform the final step in butyrate synthesis and is possible only in the presence of acetate (Louis *et al.*, 2004). Butyrate production is widely distributed among phylogenetically diverse human colonic Gram-positive *Firmicutes*. Two abundant groups are related to *Eubacterium rectale/ Roseburia* spp. and to *Faecalibacterium prausnitzii* (Louis *et al.*, 2010). While most species have the capacity for either propionate or butyrate production from hexose sugars, some species of *Lachnospiraceae* (*C. catus* and *R. inulinivorans*) have been demonstrated to switch from butyrate to propionate production on different substrates (Reichardt *et al.*, 2014; Scott *et al.*, 2006). Besides these pathways for SCFA production, there will be numerous other routes to SCFA as some microbes grow on intermediate products of fermentation, such as hydrogen gas (H_2), lactate, succinate, formate and ethanol, and convert these to end products including SCFA. Other microbes, particularly Archaea species can metabolise carbon dioxide (CO_2) either yielding methane (CH_4) or acetate.

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Dimerizzando l'acetato

Butirril-Coenzima A: Acetato-Coenzima A transferasi:
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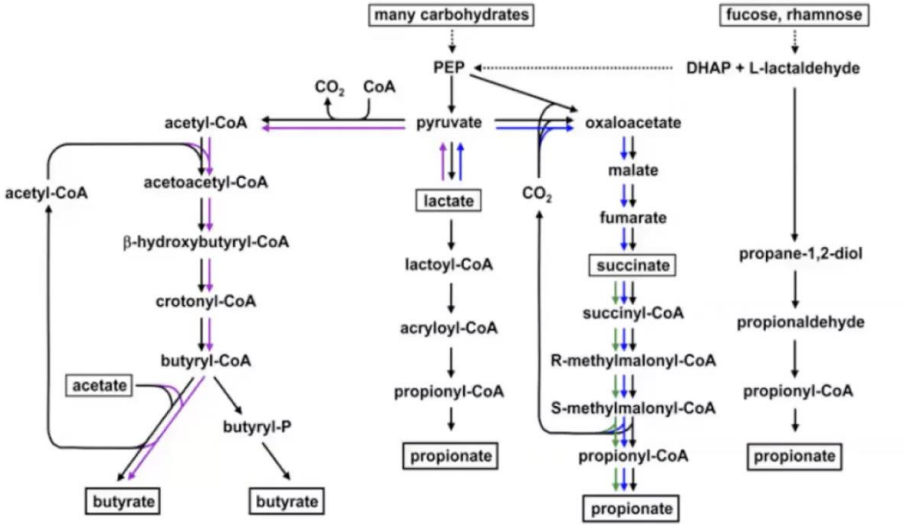
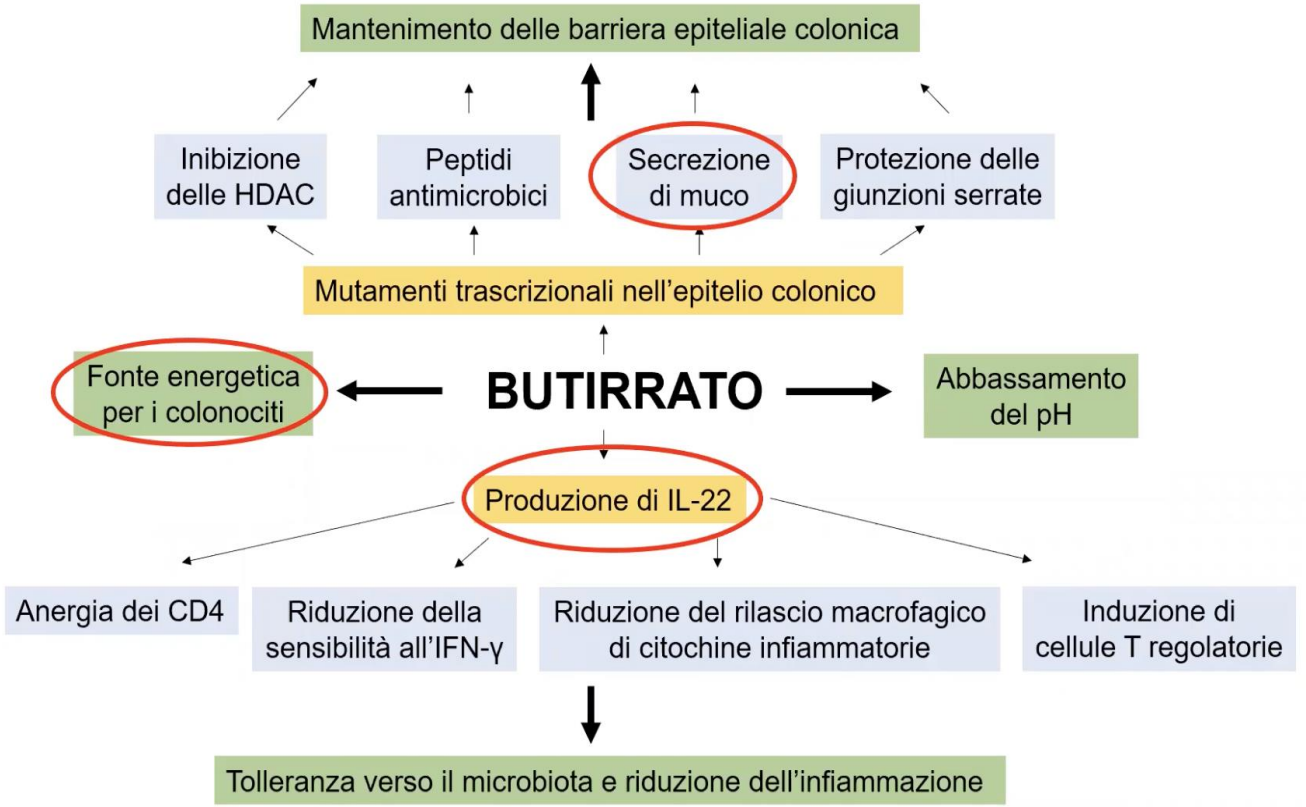
Eubacterium hallii
L'acetil-Coenzima A utilizzato da questi batteri deriva dal lattato (via dell'acrilato)

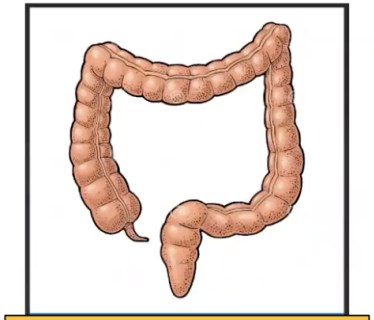
Dal lattato

H. J. Flint *et al.*



Proceedings of the Nutrition Society (2015), **74**, 13–22


Mantenimento delle barriera epiteliale colonica
Inibizione delle HDAC
Peptidi antimicrobici
Secrezione di muco
Protezione delle giunzioni serrate
Mutamenti trascrizionali nell'epitelio colonico
Fonte energetica per i colonociti
BUTIRRATO
Abbassamento del pH
Produzione di IL-22
Anergia dei CD4
Riduzione della sensibilità all'IFN-γ
Riduzione del rilascio macrofagico di citochine infiammatorie
Induzione di cellule T regolatorie
Tolleranza verso il microbiota e riduzione dell'infiammazione



IBD

↓ Biodiversità
↓ Butirrato-produttori
↓ Butirrato (B2)
↓ *B. adolescentis*

↑ Proteobacteria
↑ Gram-negatività
↑ *Bacteroides/Alistipes*
↑ *Streptococcus*
↑ *R. gnavus/R. torques*
↑ *Akkermansia*
↑ Lattato

Butirrato-produttori

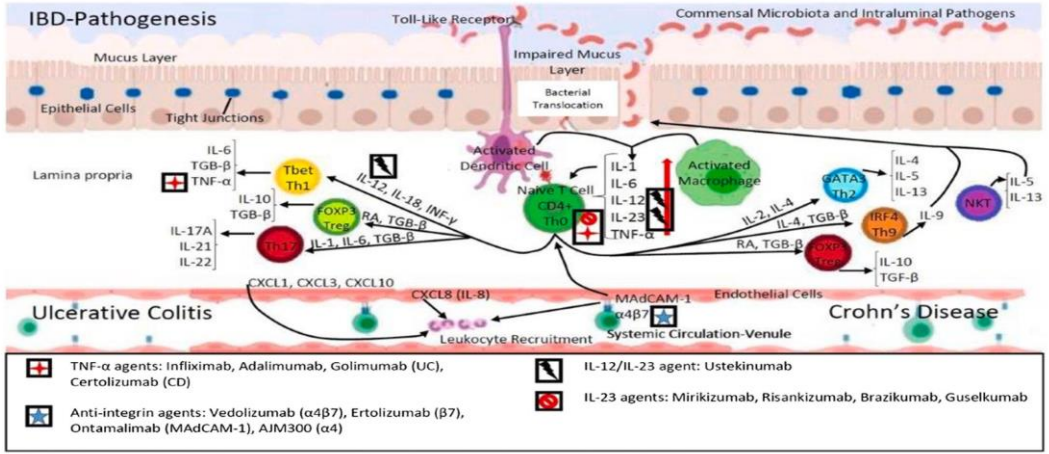
WHICH APPLICATIONS IN IBD?

Gut microbiota analysis for prediction of clinical relapse in Crohn's disease

Scientific Reports | (2022) 12:19929

Focusing on the 103 consecutive samples from 41 CD patients, we showed that the patients microbiota profiles were remarkably stable over time and associated with increasing symptom severity. Investigating further this microbiota/severity association revealed that the first signs of aggravation are (1) a loss of the main anti-inflammatory Short-Chain Fatty Acids (SCFAs) *Roseburia, Eubacterium, Subdoligranumum, Ruminococcus* ($P < 0.05$), (2) an increase in pro-inflammatory pathogens *Proteus, Finegoldia* ($P < 0.05$) while (3) an increase of other minor SCFA producers such as *Ezakiella, Anaerococcus, Megasphaera, Anaeroglobus, Fenollaria* ($P < 0.05$). Further aggravation of clinical signs is significantly linked to the subsequent loss of these minor SCFAs species and to an increase in other proinflammatory Proteobacteria such as *Klebsiella, Pseudomonas, Salmonella, Acinetobacter, Hafnia* and proinflammatory Firmicutes such as *Staphylococcus, Enterococcus, Streptococcus*. ($P < 0.05$). To our knowledge, this is the first study (1) specifically identifying subgroups of microbiota profiles in CD patients, (2) relating these groups to the evolution of symptoms over time and (3) showing a two-step process in CD symptoms' worsening. This paves the way towards a better understanding of patient-to-patient heterogeneity, as well as providing early warning signals of future aggravation of the symptoms and eventually adapting empirically treatments.

TOWARDS A PERSONALIZED IBD THERAPY

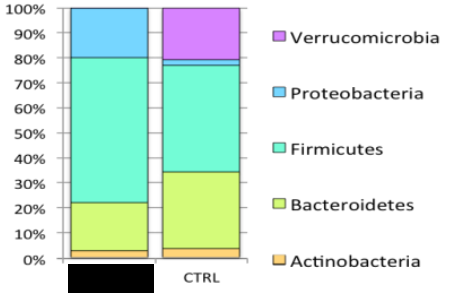


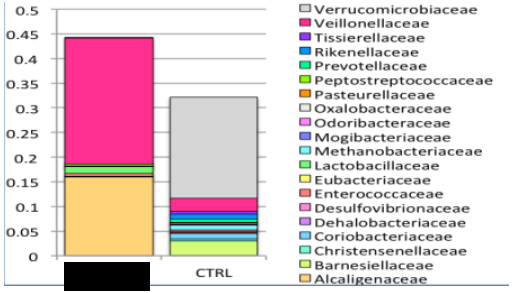
Optimize treatments → **Minimize side-effects and costs**

Moving toward a Microbiota signature for IBD patients

Nadpara et al – Dig Dis Sci 2020

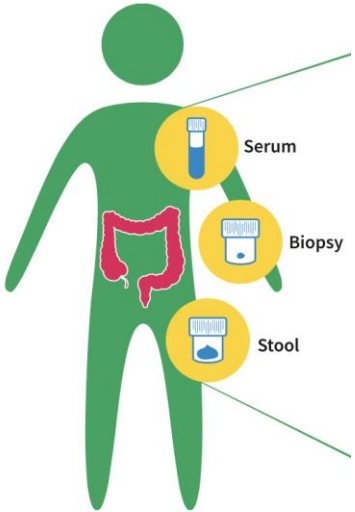
MICROBIOTA SIGNATURE:
the inflammatory microbiome of a patient with an active UC disease





Unità tassonomica	Unità tassonomica	[redacted]	CTRL	ANDAMENTO[2]
Actinobacteria	*Bifidobacterium*	0.03550	0.00621	+
Actinobacteria	*Bifidobacterium adolescentis*	0.02567	0.00027	+
Actinobacteria	*Bifidobacterium longum*	0.01599	0.00205	+
Actinobacteria	*Collinsella*	0.00092	0.00008	+
Euryarchaeota	*Methanobrevibacter*	0.00000	0.00912	-
Firmicutes	*Clostridium hiranonis*	0.00006	0.00000	+
Firmicutes	*Dorea formicigenerans*	0.00011	0.00000	+
Firmicutes	*Oscillospira*	0.00134	0.00753	-
Firmicutes	*Ruminococcus bromii*	0.00347	0.00005	+
Firmicutes	*Streptococcus*	0.00097	0.01670	-
Proteobacteria	*Acinetobacter*	0.00006	0.00001	+
Verrucomicrobia	*Akkermansia muciniphila*	0.00039	0.22569	-

MICROBIOME-ASSOCIATED BIOMARKERS IN IBD MANAGEMENT



Diagnosis
- Diagnosis
- Disease classification
- Disease activity assessment

Prognosis
- Disease recurrence prediction
- Therapeutic response

Fecal and mucosal microbiome

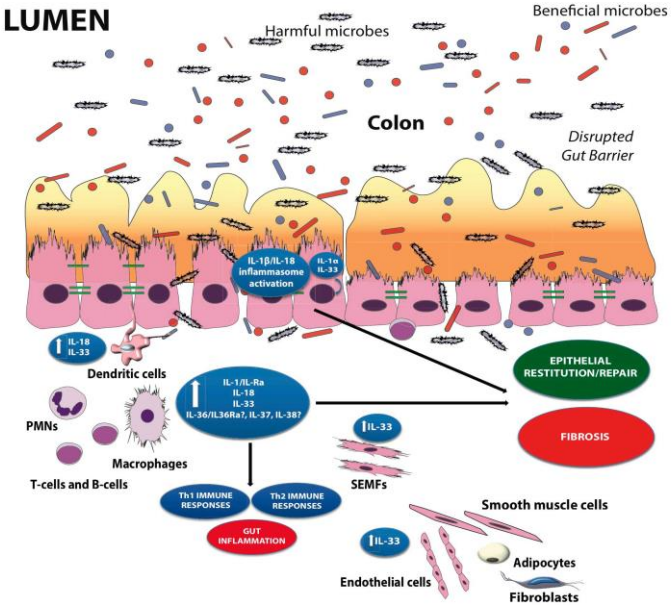
Diagnosis
Classification
Disease activity
Disease course
Recurrence after surgery
Responses to therapeutics

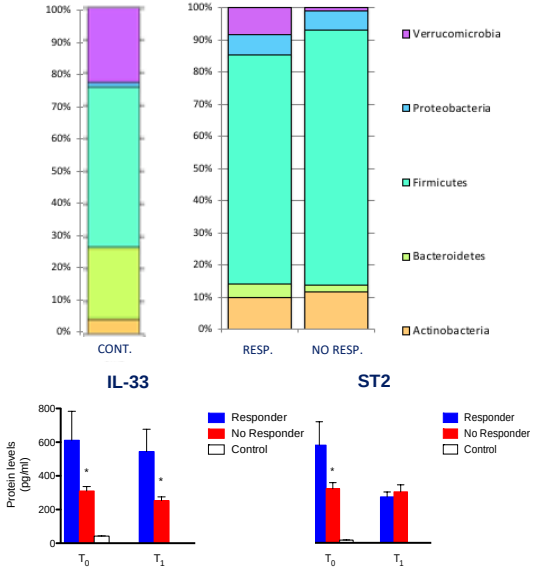
Bacteria derived metabolites,
serum and fecal microbe-associated proteins

IBD determination and classification

Caenepeel et al. - APT 2020
Zheng et al, UEGJ 2022

Microbiota-IL-33/ST2 profiling can predict mucosal response to anti-TNF in UC





Lopetuso et al, PNAS 2018
Lopetuso et al, unpublished data

Microbiota and IBD

Gut microbiota composition is altered in IBD vs controls

Gut microbiota composition is altered in active vs non-active IBD

Gut microbiota can influence the development of IBD

IBD changes when targeting microbiota

Therapeutic microbiota modulation

Diet & nutritional support

- Caloric amount, minerals, vitamins
- Diet composition (fibers/high glicemic index/saturated fatty acids…)

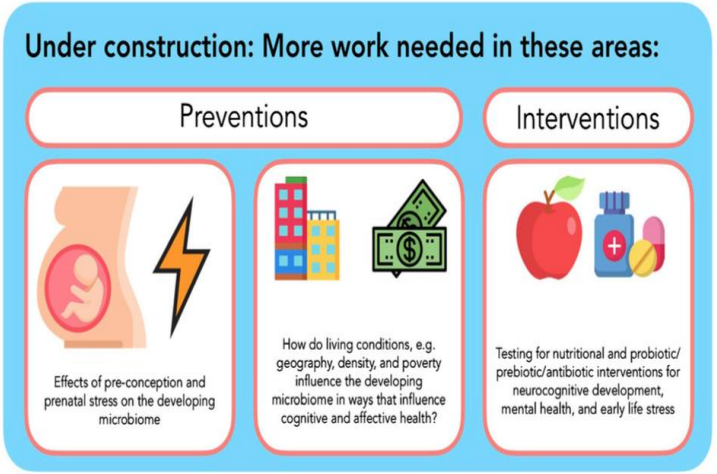
Removal of predisposing conditions

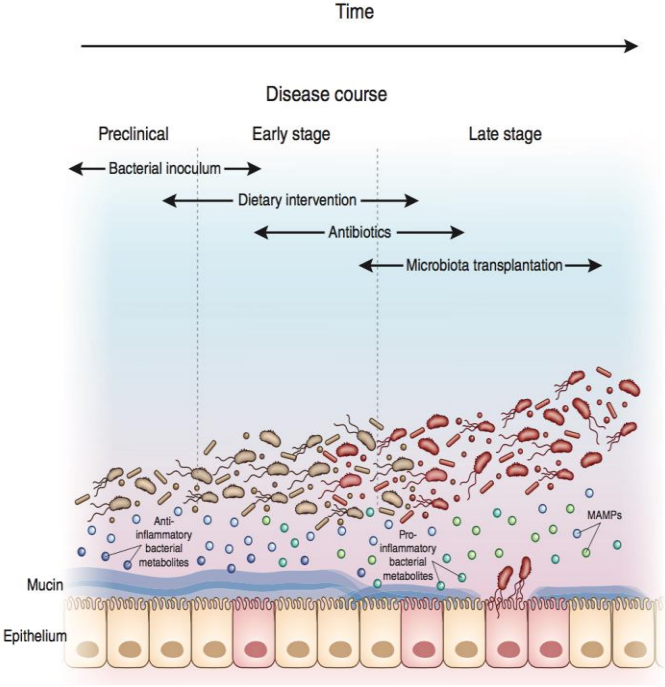
- Treat diabetes, endocrine, other motility disorders..
- Surgery or prokinetics when indicated

Therapeutic interventions

- Antibiotics
- Prebiotics, probiotics, postbiotics, symbiotics
- Fecal Microbiota Transplantation

Designing strategies for reconfiguring homeostasis





Vogel et al 2020
Tamburini et al 2016