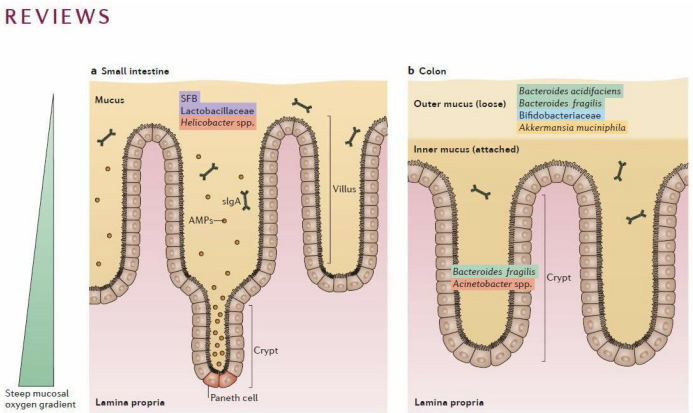
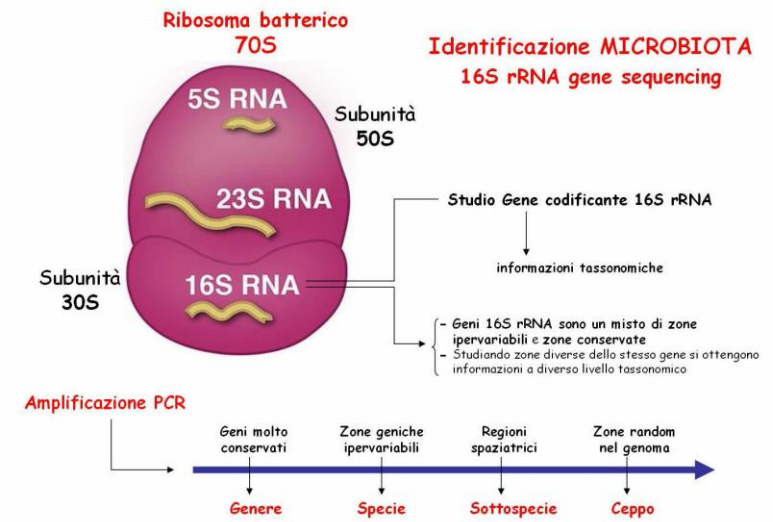
Biologia di Laboratorio
MICROBIOTA le più comuni Patologie da DISBIOSI





Enpab webinar

Webinar ECM
8 Ottobre 2020 - ore 10.00 – 12.30

Mauro Mario Amato

LISTA NUMERO UNO – Consiglio di Amministrazione Enpab

Tornata elettorale 2020 – 2025

Noi per i Biologi
Enpab
con
Tiziana Stallone

CANDIDATI

ALTOMARI Santo	CORIGLIANO CALABRO (CS)	10/03/1949
CAPURSO Serena	ROMA (RM)	10/09/1981
IMPERADORI Laura	BRENO (BS)	23/02/1978
MICIELI Maria Grazia	NOTO (SR)	16/03/1963
ORTENSI Ilaria	ROMA (RM)	16/12/1978
PETRILLO Giovanbattista	CASERTA (CE)	06/01/1959
STALLONE Tiziana	ROMA (RM)	17/03/1972

Problemi → Soluzione
Successo

LISTA NUMERO UNO – Consiglio di Indirizzo Generale Enpab

Tornata elettorale 2020 – 2025

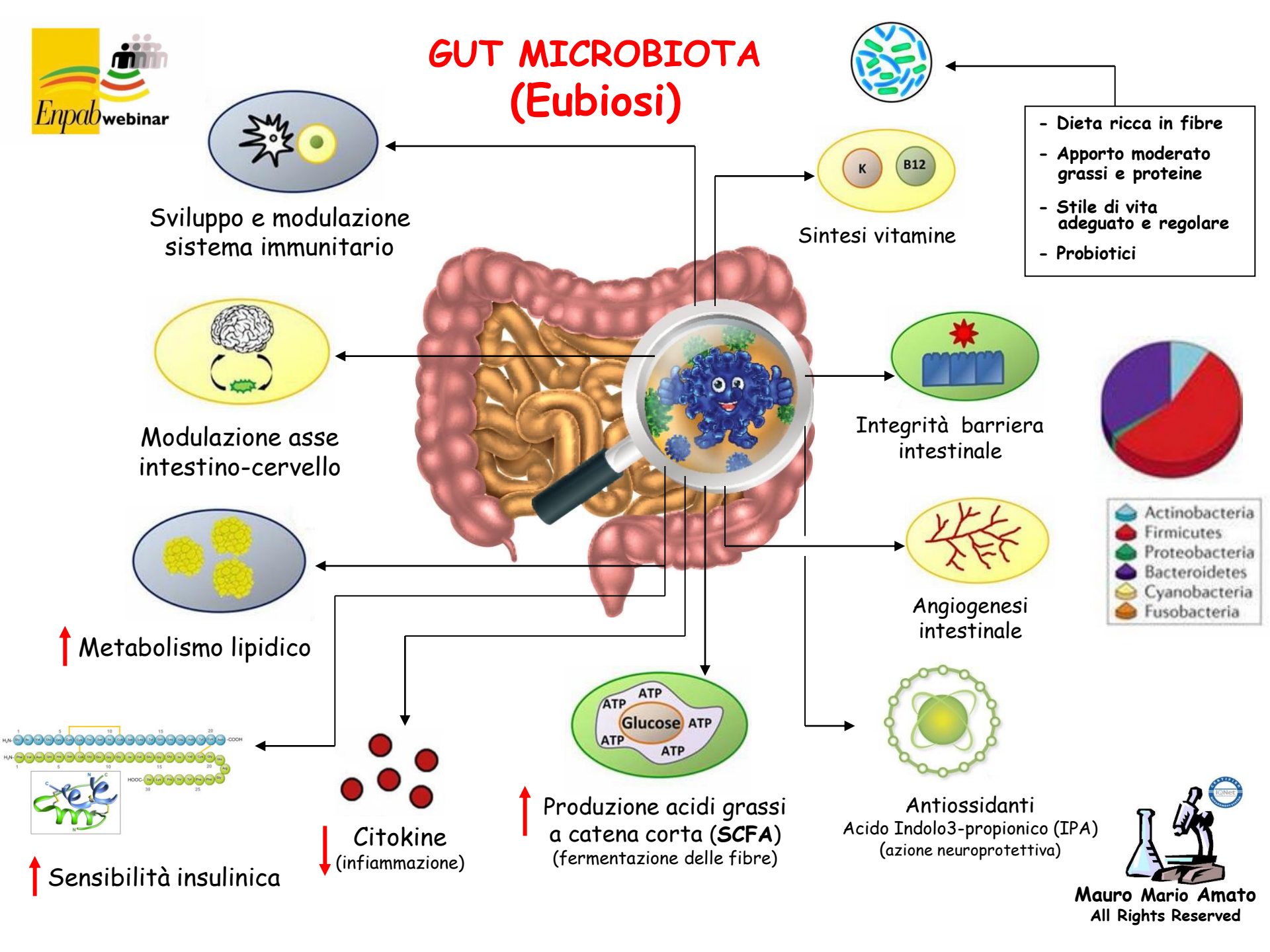
LISTA

Noi per i Biologi
Enpab
con
Tiziana Stallone

CANDIDATI

BALDI Marina	ROMA (RM)	01/05/1958
BONUCCI Francesco	FORLI' (FC)	18/08/1964
BRIGANDI' Simona	MESSINA (ME)	06/03/1979
CASACCIA Roberto	ROMA (RM)	15/01/1959
CROCI Sonia	SAN BENEDETTO DEL TRONTO (AP)	28/11/1984
CUTINI Laura	GROSSETO (GR)	19/10/1953
DORE Cristina	NUORO (NU)	13/05/1972
ERCOLANO Salvatore	VICO EQUENSE (NA)	25/06/1987
ETTORRE Michele	TARANTO (TA)	01/01/1954
GATTO Emilio	PERITO (SA)	21/03/1948
LA MURA Enrico	POMPEI (NA)	14/05/1949
LENOCI Rosa	MASSAFRA (TA)	20/01/1960
MUTO Ornella	MESSINA (ME)	29/09/1988
NUTINI Lucia	FIRENZE (FI)	21/12/1958
RAGO Ciriaco	BATTIPAGLIA (SA)	02/05/1948
RUVOLO Giovanni	CALTANISSETTA (CL)	08/05/1966
SORRENTI Massimo	SIRACUSA (SR)	17/09/1963
TAFURI Nicola	MUGNANO DI NAPOLI (NA)	07/09/1960
TONELLATO Luigi	BELGIO (EE)	30/05/1956
ZAMBRANO Angelina	MERCATO SAN SEVERINO (SA)	10/01/1951
ZOCCHI Gianni	FIRENZE (FI)	16/11/1955

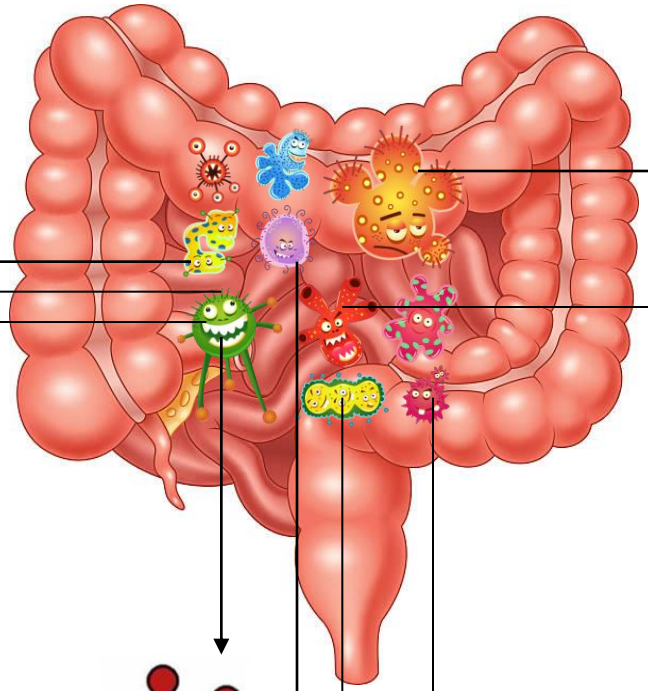
GUT MICROBIOTA
(Eubiosi)

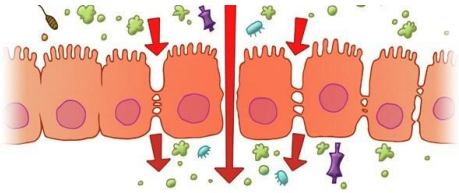


GUT MICROBIOTA
(Disbiosi)

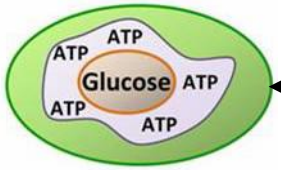
- Dieta ricca zuccheri e acidi grassi saturi
- Consumo eccessivo di proteine
- Alterazione pH
- Antibiotici e inibitori di pompa protonica

Riduzione progressina anaerobi





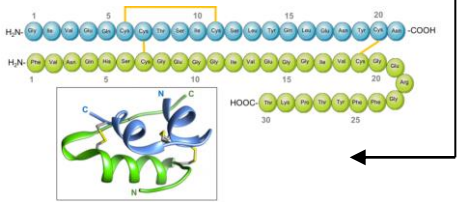
Permeabilità intestinale



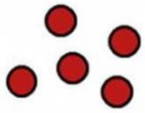
↓ Produzione acidi grassi a catena corta (**SCFA**) (fermentazione delle fibre)

↑ Rischio MICI/IBS

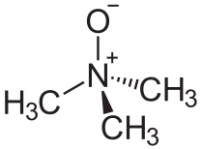
↑ Rischio CVD



↑ Resistenza insulinica (DMT2)

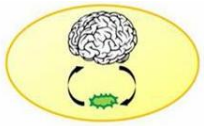


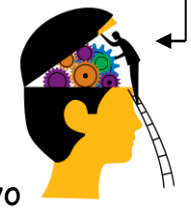
↑ Citokine (infiammazione intestinale)



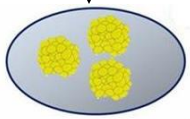
↑ Produzione TMAO (trimetilannina N-ossido)

↑ Produzione Lipopolisaccaridi





↓ Declino cognitivo



↓ Metabolismo lipidico

Antiossidanti ↓

Enpab webinar

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ORMONI INTESTINALI

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Rilasciato post-prandium a livello di ileo/colon in risposta a nutrienti, come il glucosio, per **aumentare l'insulina e inibire la secrezione di glucagone**. **Inibisce lo svuotamento gastrico e influenza sazietà e assunzione di cibo**

Rilasciato insieme al GLP1 **regola assunzione di cibo e sazietà** attraverso l'**attivazione dei recettori Y2 nel nucleo arcuato ipotalamico**

GLP-1 **(Peptide1 Glucagone simile)**

PYY **(Peptide tirosina-tirosina)**

5-HT **(Serotonina)**

GIP **(Peptide Insulinotropico glucosio-dipendente)**

CCK **(Colecistochinina)**

Prodotta dalle **cellule enterocromaffini** (EC circa il 50% delle entero-endocrine) rappresenta il 95 % della serotonina all'interno del corpo.
Le EC sono disperse su tutta la lunghezza del tratto gastrointestinale e svolgono **azioni importanti associate alla motilità** rilevando l'ambiente nutriente locale e secernendo serotonina.

E' una incretina con **azione simile al GLP1** rilasciata post-prandium dagli enterociti endocrni K dell'intestino tenue.
E' stato **notato** che un suo **incremento** sia **associato all'aumento di adiposità**

Prodotta prevalentemente intestino tenue superiore in risposta al grasso alimentare e apporto proteico.
Ruoli ben definiti nella **regolazione dell'appetito, svuotamento gastrico, motilità e rilascio di acidi biliari e pancreatici**

Enpab webinar

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US National Library of Medicine
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Enpab webinar

Journal List > Front Physiol > v.10; 2019 > PMC6477058

frontiers in Physiology

Front Physiol. 2019; 10: 428.
Published online 2019 Apr 16. doi: 10.3389/fphys.2019.00428

PMCID: PMC6477058
PMID: 31057420

The Influence of the Gut Microbiome on Host Metabolism Through the Regulation of Gut Hormone Release

Alyce M. Martin,[1] Emily W. Sun,[1] Geraint B. Rogers,[2,3] and Damien J. Keating[1,4,*]

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Microbioma e Metabolismo attraverso gli ormoni intestinali

This article has been cited by other articles in PMC.

Abstract

Go to:

The microbial community of the gut conveys significant benefits to host physiology. A clear relationship has now been established between gut bacteria and host metabolism in which microbial-mediated gut hormone release plays an important role. Within the gut lumen, bacteria produce a number of metabolites and contain structural components that act as signaling molecules to a number of cell types within the mucosa. Enteroendocrine cells within the mucosal lining of the gut synthesize and secrete a number of hormones including CCK, PYY, GLP-1, GIP, and 5-HT, which have regulatory roles in key metabolic processes such as insulin sensitivity, glucose tolerance, fat storage, and appetite. Release of these hormones can be influenced by the presence of bacteria and their metabolites within the gut and as such, microbial-mediated gut hormone release is an important component of microbial regulation of host metabolism. Dietary or pharmacological interventions which alter the gut microbiome therefore pose as potential therapeutics for the treatment of human metabolic disorders. This review aims to describe the complex interaction between intestinal microbiota and their metabolites and gut enteroendocrine cells, and highlight how the gut microbiome can influence host metabolism through the regulation of gut hormone release.

Front Physiol

Front Physiol

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6477058/

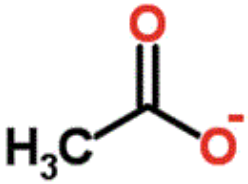
DISBIOSI

Acidi grassi a catena corta fecali (Fecal **SCFA**)
(**fermentazione delle fibre**)

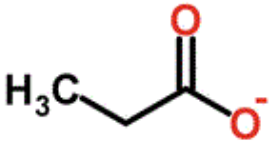
campione feci

trattamento

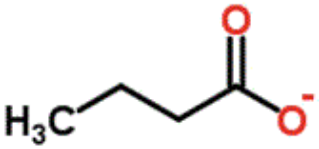
Gas-cromatografia



Acetato



Propionato



Butirrato

- Il **consumo di fibre** favorisce la crescita di batteri sani come Lattobacilli, Bifidobatteri e Prevotella inibendo la proliferazione di E.coli e Salmonella
- Ruolo **benefico sulla permebilità intestinale** aumentano la diversità delle specie batteriche
- Capacità di **inibire la produzione citochine pro-infiammatorie** come NF-κB, IFN-γ e TNF-α
- **Attività antitumorale** con modulazione della HDAC (Istone Deacetilasi) e inibizione della proliferazione cellulare e apoptosi.
- Nelle **MICI** evidenziata **scarsa produzione di butirrato disbiosi-dipendente**

Mauro Mario Amato
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Enpab webinar

Ruolo chiave dei SCFAs nel dialogo Intestino-Cervello

Mauro Amato

nature reviews gastroenterology & hepatology

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Review Article | Published: 23 May 2019

The role of short-chain fatty acids in microbiota–gut–brain communication

Boushra Dalile, Lukas Van Oudenhove, Bram Vervliet & Kristin Verbeke

Nature Reviews Gastroenterology & Hepatology **16**, 461–478(2019) | Cite this article

14k Accesses | **93** Citations | **275** Altmetric | Metrics

https://www.nature.com/articles/s41575-019-0157-3

Abstract

Short-chain fatty acids (SCFAs), the main metabolites produced by bacterial fermentation of dietary fibre in the gastrointestinal tract, are speculated to have a key role in microbiota–gut–brain crosstalk. However, the pathways through which SCFAs might influence psychological functioning, including affective and cognitive processes and their neural basis, have not been fully elucidated. Furthermore, research directly exploring the role of SCFAs as potential mediators of the effects of microbiota-targeted interventions on affective and cognitive functioning is sparse, especially in humans. This Review summarizes existing knowledge on the potential of SCFAs to directly or indirectly mediate microbiota–gut–brain interactions. The effects of SCFAs on cellular systems and their interaction with gut–brain signalling pathways including immune, endocrine, neural and humoral routes are described. The effects of microbiota-targeted interventions such as prebiotics, probiotics and diet on psychological functioning and the putative mediating role of SCFA signalling will also be discussed, as well as the relationship between SCFAs and psychobiological processes. Finally, future directions to facilitate direct investigation of the effect of SCFAs on psychological functioning are outlined.

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Journal List › Biosci Microbiota Food Health › v.39(1); 2020 › PMC6971417

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6971417/

BMFH Bioscience of Microbiota,Food and Health

BMFH Press | BMFH home | For Authors | Submissions

Biosci Microbiota Food Health. 2020; 39(1): 11–17.
Published online 2019 Oct 5. doi: 10.12938/bmfh.19-010

PMCID: PMC6971417
PMID: 32010539

Associations of gut microbiota, dietary intake, and serum short-chain fatty acids with fecal short-chain fatty acids

Ryodai YAMAMURA,[1] Koshi NAKAMURA,[2,3,*] Naoya KITADA,[4] Tomoyasu AIZAWA,[5] Yu SHIMIZU,[4] Kiminori NAKAMURA,[5] Tokiyoshi AYABE,[5] Takashi KIMURA,[3] and Akiko TAMAKOSHI[3]

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Associated Data

Supplementary Materials

Abstract

Go to:

In recent years, short-chain fatty acids (SCFAs) have been reported to play an important role in maintaining human health. Fecal SCFA concentrations correlate well with colonic SCFA status and gut microbiota composition. However, the associations with the gut microbiota functional pathway, dietary intake, blood SCFAs, and fecal SCFAs remain uncertain. To clarify these relationships, we collected fecal samples, blood samples, and dietary habit data from 12 healthy adults aged 22–51 years. The relative abundance of several SCFA-producing bacteria, gut microbiota diversity, and functional pathways related to SCFA biosynthesis were positively associated with fecal SCFAs even after adjusting for age and sex. Furthermore, fecal acetate was likely to be positively associated with serum acetate. By contrast, dietary intake was not associated with fecal SCFAs. Overall, the present study highlights the potential usefulness of fecal SCFAs as an indicator of the gut microbiota ecosystem and dynamics of SCFAs in the human body.

Enpab webinar

Associazione microbiota, apporto dietetico e SCFA fecali/sierici

SCFA fecali come **indicatore** dell'ecosistema del **microbiota intestinale** e delle **dinamiche degli SCFA** nel corpo umano.

Mauro Amato

NCBI Resources How To

PMC US National Library of Medicine National Institutes of Health

PMC | Advanced | Journal list

Journal List > Gut Microbes > v.7(3); 2016 > PMC4939913

gut microbes

Gut Microbes. 2016; 7(3): 189–200.
Published online 2016 Mar 10. doi: 10.1080/19490976.2015.1134082

PMCID: PMC4939913
PMID: 26963409

Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism

Douglas J. Morrison and Tom Preston

Author information · Article notes · Copyright and License information Disclaimer

This article has been cited by other articles in PMC.

ABSTRACT

Go to:

The formation of SCFA is the result of a complex interplay between diet and the gut microbiota within the gut lumen environment. The discovery of receptors, across a range of cell and tissue types for which short chain fatty acids SCFA appear to be the natural ligands, has led to increased interest in SCFA as signaling molecules between the gut microbiota and the host. SCFA represent the major carbon flux from the diet through the gut microbiota to the host and evidence is emerging for a regulatory role of SCFA in local, intermediary and peripheral metabolism. However, a lack of well-designed and controlled human studies has hampered our understanding of the significance of SCFA in human metabolic health. This review aims to pull together recent findings on the role of SCFA in human metabolism to highlight the multi-faceted role of SCFA on different metabolic systems.

Gut Microbes

Ruolo chiave SCFAs metabolismo locale, intermedio e periferico

Mauro Amato

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4939913/

Springer CURRENT NUTRITION REPORTS
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Ruolo chiave SCFAs nella espressione effetti benefici sul metabolismo e salute cardiovascolare

Mauro Amato

Curr Nutr Rep. 2018; 7(4): 198–206.
Published online 2018 Sep 28. doi: 10.1007/s13668-018-0248-8
PMCID: PMC6244749
PMID: 30264354

Role of Gut Microbiota-Generated Short-Chain Fatty Acids in Metabolic and Cardiovascular Health

Edward S. Chambers,[1] Tom Preston,[2] Gary Frost,[1] and Douglas J. Morrison[2]

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This article has been cited by other articles in PMC.

Springer Open Choice

Abstract

Go to:

Purpose of this Review

This review assesses the latest evidence linking short-chain fatty acids (SCFA) with host metabolic health and cardiovascular disease (CVD) risk and presents the latest evidence on possible biological mechanisms.

Recent Findings

SCFA have a range of effects locally in the gut and at both splanchnic and peripheral tissues which together appear to induce improved metabolic regulation and have direct and indirect effects on markers of CVD risk.

Summary

SCFA produced primarily from the microbial fermentation of dietary fibre appear to be key mediators of the beneficial effects elicited by the gut microbiome. Not only does dietary fibre fermentation regulate microbial activity in the gut, SCFA also directly modulate host health through a range of tissue-specific mechanisms related to gut barrier function, glucose homeostasis, immunomodulation, appetite regulation and obesity. With the increasing burden of obesity worldwide, the role for gut microbiota-generated SCFA in protecting against the effects of energy dense diets offers an intriguing new avenue for regulating metabolic health and CVD risk.

Springer Open Choice

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6244749/

DISBIOSI

↑ **TMA**
(trimetilamina)

campione
feci

trattamento

(HPLC-MS)
High-Performance Liquid Chromatography
Mass Spectrometry

Dosaggio

fegato → Flavina Monoossigenai 3 → **TMAO**
(trimetilamina-Ossido)

plasma

Immunochimica

- **TMA** prodotta dal metabolismo batterico intestinale durante la digestione della colina, lecitina e carnitina presenti nelle **carni rosse**, fegato, uova e altri prodotti animali.
  L'aumentato consumo favorisce lo sviluppo di flora TMA-produttore (**Proteus, Desulfovibrio, Klebsiella**)

- L'**aumento** della **concentrazione è aterogenica** e **correlata** non solo alle **CVD** e **Ictus** ma anche alla **Sindrome Metabolica**

- **Aumento concentrazione** TMAO si associa anche alle **malattie renali**, al **Diabete tipo 2** alla **morte precoce per qualsiasi causa**

- Evidenziato **dosaggio triplicato** nei i **soggetti con dieta ricca di carne rossa** rispetto alla dieta ricca di carni bianche o proteine per vegetali.

Mauro Mario Amato
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Enpab webinar

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Journal List › Nutrients › v.10(10); 2018 Oct › PMC6213249

Enpab webinar

nutrients MDPI

Nutrients. 2018 Oct; 10(10): 1398.
Published online 2018 Oct 1. doi: 10.3390/nu10101398

PMCID: PMC6213249
PMID: 30275434

Implication of Trimethylamine N-Oxide (TMAO) in Disease: Potential Biomarker or New Therapeutic Target

Manuel H. Janeiro,[1,2] María J. Ramírez,[1,2] Fermín I. Milagro,[3,4] J. Alfredo Martínez,[3,4,5] and Maite Solas[1,2,*]

Author information · Article notes · Copyright and License information Disclaimer

This article has been cited by other articles in PMC.

Correlazone diretta
TMAO/Eventi CVD avversi maggiori
TMAO/Disturbi Neurologici

Abstract

Go to:

Trimethylamine N-oxide (TMAO) is a molecule generated from choline, betaine, and carnitine via gut microbial metabolism. The plasma level of TMAO is determined by several factors including diet, gut microbial flora, drug administration and liver flavin monooxygenase activity. In humans, recent clinical studies evidence a positive correlation between elevated plasma levels of TMAO and an increased risk for major adverse cardiovascular events. A direct correlation between increased TMAO levels and neurological disorders has been also hypothesized. Several therapeutic strategies are being explored to reduce TMAO levels, including use of oral broad spectrum antibiotics, promoting the growth of bacteria that use TMAO as substrate and the development of target-specific molecules. Despite the accumulating evidence, it is questioned whether TMAO is the mediator of a bystander in the disease process. Thus, it is important to undertake studies to establish the role of TMAO in human health and disease. In this article, we reviewed dietary sources and metabolic pathways of TMAO, as well as screened the studies suggesting possible involvement of TMAO in the etiology of cardiovascular and neurological disorders, underlying the importance of TMAO mediating inflammatory processes. Finally, the potential utility of TMAO as therapeutic target is also analyzed.

Mauro Amato

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6213249/

nutrients

MDPI

Enpab webinar

Article

Trimethylamine-N-oxide (TMAO) as Novel Potential Biomarker of Early Predictors of Metabolic Syndrome

Luigi Barrea [1,*,†], Giuseppe Annunziata [2,†], Giovanna Muscogiuri [1], Carolina Di Somma [3], Daniela Laudisio [1], Maria Maisto [2], Giulia de Alteriis [1], Gian Carlo Tenore [2], Annamaria Colao [1] and Silvia Savastano [1]

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2 Department of Pharmacy, University of Naples "Federico II", Via Domenico Montesano 49, 80131 Naples, Italy; giuseppe.annunziata@unina.it (G.A.); maria.maisto@unina.it (M.M.); giancarlo.tenore@unina.it (G.C.T.)

3 IRCCS SDN, Napoli Via Gianturco 113, 80143 Naples, Italy; cdisomma@unina.it

* Correspondence: luigi.barrea@unina.it; Tel.: +39-081-746-3779

† These Authors contributed equally to this work.

Received: 14 November 2018; Accepted: 11 December 2018; Published: 13 December 2018

check for updates

Abstract: There is a mechanistic link between the gut-derived metabolite trimethylamine-N-oxide (TMAO) and obesity-related diseases, suggesting that the TMAO pathway may also be linked to the pathogenesis of obesity. The Visceral Adiposity Index (VAI), a gender-specific indicator of adipose dysfunction, and the Fatty Liver Index (FLI), a predictor of non-alcoholic fatty liver disease (NAFLD), are early predictors of metabolic syndrome (MetS). In this cross-sectional observational study, we investigated TMAO levels in adults stratified according to Body Mass Index (BMI) and the association of TMAO with VAI and FLI. One hundred and thirty-seven adult subjects (59 males; 21–56 years) were enrolled. TMAO levels were detected using HPLC/MS analysis. Homeostatic Model Assessment of Insulin Resistance (HoMA-IR), VAI and FLI were included as cardio-metabolic indices. TMAO levels increased along with BMI and were positively associated with VAI and FLI, independently, on common potential covariates. The most sensitive and specific cut-offs for circulating levels of TMAO to predict the presence of NAFLD-FLI and MetS were $\geq$8.02 μM and $\geq$8.74 μM, respectively. These findings allow us to hypothesize a role of TMAO as an early biomarker of adipose dysfunction and NAFLD-FLI in all borderline conditions in which overt MetS is not present, and suggest that a specific cut-off of TMAO might help in identifying subjects at high risk of NAFLD.

TMAO
marcatore precoce per la Sindrome Metabolica

Mauro Amato

https://www.researchgate.net/publication/329649472_Trimethylamine-N-oxide_TMAO_as_Novel_Potential_Biomarker_of_Early_Predictors_of_Metabolic_Syndrome

DISBIOSI

laboratorio → **Dosaggio Immunochimico**

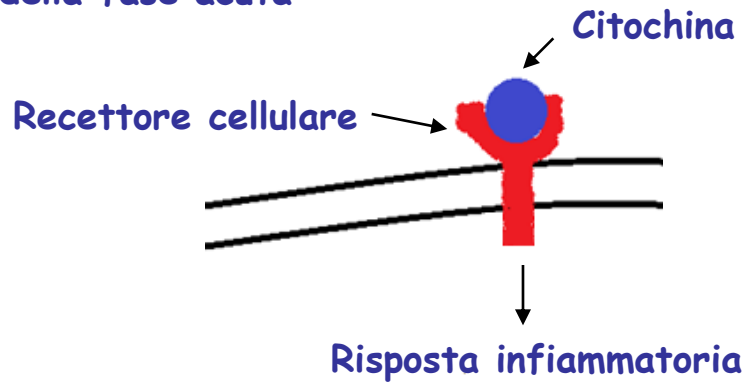
↑ **Citochine** → **IL-1**, **TNFα**, **IL-6**

infiammatorie primarie

- Citochina secreta da vari tipi cellulari (macrofagi, monociti, cellule dendritiche, fibroblasti e cellule endoteliali) **spettro di azione su grande varietà di cellule/tessuti**
- **Stimola il fegato a produrre le proteine di fase acuta**

- Citochina prodotta da leucociti attivati è implicata nella **regolazione della risposta immunitaria**
- **Marcatore** di attivazione del sistema immunitario
- **Stimola** inoltre la produzione delle **proteine della fase acuta**

Citochina coinvolta nella **risposta infiammatoria e nell'induzione di apoptosi.**



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Journal List › HHS Author Manuscripts › PMC5131922

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HHS Public Access
Author manuscript
Peer-reviewed and accepted for publication

About author manuscripts | Submit a manuscript

Author Manuscript

Cell. Author manuscript; available in PMC 2017 Nov 3.
Published in final edited form as:
Cell. 2016 Nov 3; 167(4): 1125–1136.e8.
doi: 10.1016/j.cell.2016.10.020

PMCID: PMC5131922
NIHMSID: NIHMS825283
PMID: 27814509

Linking the Human Gut Microbiome to Inflammatory Cytokine Production Capacity

Melanie Schirmer,[1,2] Sanne P. Smeekens,[3] Hera Vlamakis,[1] Martin Jaeger,[3] Marije Oosting,[3] Eric A. Franzosa,[1,2] Rob ter Horst,[3] Trees Jansen,[3] Liesbeth Jacobs,[3] Marc Jan Bonder,[4] Alexander Kurilshikov,[4,5,6] Jingyuan Fu,[4,7] Leo A.B. Joosten,[3] Alexandra Zhernakova,[4] Curtis Huttenhower,[1,2] Cisca Wijmenga,[4] Mihai G. Netea,[3,*] and Ramnik J. Xavier[1,8,9,10,11,*]

Disbiosi e produzione anormale di citochine proinfiammatorie

Summary

Go to:

Gut microbial dysbioses are linked to aberrant immune responses, which are often accompanied by abnormal production of inflammatory cytokines. As part of the Human Functional Genomics Project (HFGP), we investigate how differences in composition and function of gut microbial communities may contribute to inter-individual variation in cytokine responses to microbial stimulations in healthy humans. We observe microbiome-cytokine interaction patterns that are stimulus-specific, cytokine-specific, and cytokine- and stimulus-specific. Validation of two predicted host-microbial interactions reveal that TNFα and IFNγ production are associated with specific microbial metabolic pathways: palmitoleic acid metabolism and tryptophan degradation to tryptophol. Besides providing a resource of predicted microbially-derived mediators that influence immune phenotypes in response to common microorganisms, these data can help to define principles for understanding disease susceptibility. The three HFGP studies presented in this issue lay the groundwork for further studies aimed at understanding the interplay between microbial, genetic, and environmental factors in the regulation of the immune response in humans.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5131922/

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Journal List › Int J Mol Sci › v.20(3); 2019 Feb › PMC6387318

International Journal of Molecular Sciences — MDPI

Int J Mol Sci. 2019 Feb; 20(3): 501.
Published online 2019 Jan 24. doi: 10.3390/ijms20030501

PMCID: PMC6387318
PMID: 30682772

The Interplay between Immunity and Microbiota at Intestinal Immunological Niche: The Case of Cancer

Rossella Cianci,[1,*] Laura Franza,[1] Giovanni Schinzari,[2] Ernesto Rossi,[2] Gianluca Ianiro,[3] Giampaolo Tortora,[2] Antonio Gasbarrini,[3] Giovanni Gambassi,[1] and Giovanni Cammarota[3]

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Interazione Microbiota-Immunità (in caso di cancro)

This article has been cited by other articles in PMC.

Abstract

Go to:

The gut microbiota is central to the pathogenesis of several inflammatory and autoimmune diseases. While multiple mechanisms are involved, the immune system clearly plays a special role. Indeed, the breakdown of the physiological balance in gut microbial composition leads to dysbiosis, which is then able to enhance inflammation and to influence gene expression. At the same time, there is an intense cross-talk between the microbiota and the immunological niche in the intestinal mucosa. These interactions may pave the way to the development, growth and spreading of cancer, especially in the gastro-intestinal system. Here, we review the changes in microbiota composition, how they relate to the immunological imbalance, influencing the onset of different types of cancer and the impact of these mechanisms on the efficacy of traditional and upcoming cancer treatments.

Int J Mol Sci

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6387318/

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Journal List › Front Microbiol › v.9; 2018 › PMC5797576

frontiers in Microbiology

Front Microbiol. 2018; 9: 61.
Published online 2018 Jan 30. doi: 10.3389/fmicb.2018.00061

PMCID: PMC5797576
PMID: 29441049

Intestinal Microbiome Shifts, Dysbiosis, Inflammation, and Non-alcoholic Fatty Liver Disease

Emma T. Saltzman,[1,2,*] Talia Palacios,[1,2] Michael Thomsen,[1,2] and Luis Vitetta[1,2,*]

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Abstract

Go to:

Adverse fluctuations in the distribution of the intestinal microbiome cohort has been associated with the onset of intra- and extra-intestinal inflammatory conditions, like the metabolic syndrome (MetS) and it's hepatic manifestation, non-alcoholic fatty liver disease (NAFLD). The intestinal microbial community of obese compared to lean subjects has been shown to undergo configurational shifts in various genera, including but not limited to increased abundances of *Prevotella, Escherichia, Peptoniphilus*, and *Parabacteroides* and decreased levels of *Bifidobacteria, Roseburia*, and *Eubacteria* genera. At the phylum level, decreased *Bacteroidetes* and increased *Firmicutes* have been reported. The intestinal microbiota therefore presents an important target for designing novel therapeutic modalities that target extra-intestinal inflammatory disorders, such as NAFLD. This review hypothesizes that disruption of the intestinal–mucosal macrophage interface is a key factor in intestinal-liver axis disturbances. Intestinal immune responses implicated in the manifestation, maintenance and progression of NAFLD provide insights into the dialogue between the intestinal microbiome, the epithelia and mucosal immunity. The pro-inflammatory activity and immune imbalances implicated in NAFLD pathophysiology are reported to stem from dysbiosis of the intestinal epithelia which can serve as a source of hepatoxic effects. We posit that the hepatotoxic consequences of intestinal dysbiosis are compounded through intestinal microbiota-mediated

Front Microbiol

Front Microbiol

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Correlazione Microbiota/Infiammazione/NAFLD

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Journal List › Microorganisms › v.7(8); 2019 Aug › PMC6722800

microorganisms MDPI

Microorganisms. 2019 Aug; 7(8): 271.
Published online 2019 Aug 19. doi: 10.3390/microorganisms7080271

PMCID: PMC6722800
PMID: 31430948

The Role of Gut Microbiota in Intestinal Inflammation with Respect to Diet and Extrinsic Stressors

Stefani Lobionda, Panida Sittipo, Hyog Young Kwon,* and Yun Kyung Lee*

Author information ▸ Article notes ▸ Copyright and License information Disclaimer

This article has been cited by other articles in PMC.

Abstract

Go to:

The gut microbiota maintains a symbiotic relationship with the host and regulates several important functions including host metabolism, immunity, and intestinal barrier function. Intestinal inflammation and inflammatory bowel disease (IBD) are commonly associated with dysbiosis of the gut microbiota. Alterations in the gut microbiota and associated changes in metabolites as well as disruptions in the intestinal barrier are evidence of the relationship between the gut microbiota and intestinal inflammation. Recent studies have found that many factors may alter the gut microbiota, with the effects of diet being commonly-studied. Extrinsic stressors, including environmental stressors, antibiotic exposure, sleep disturbance, physical activity, and psychological stress, may also play important roles in altering the composition of the gut microbiota. Herein, we discuss the roles of the gut microbiota in intestinal inflammation in relation to diet and other extrinsic stressors.

Correlazione Microbiota/Infiammazione Intestinale in relazione a Dieta/Stress estrinseco

Mauro Amato

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6722800/

DISBIOSI

↑ Resistenza Insulinica

- **Clamp Euglicemico-iperinsulinemico**
  (Test gold-standard abbastanza invasivo)
- **Curva Insulinemica da carico orale di glucosio**

Funzioni matematiche

HOMA-IR (Homeostasis Model Assessment – Insulin Resistance)
HOMA-β (Homeostasis Model Assessment – β cell function)
Indice QUICKI (Quantitative Insulin sensitivity Check Index)

InsuTAG
TyG Index (Indice Trigliceridi-Glucosio)
Trigliceridi/HDL Ratio (Rapporto Trigliceridi-HDL-Colesterolo a digiuno)

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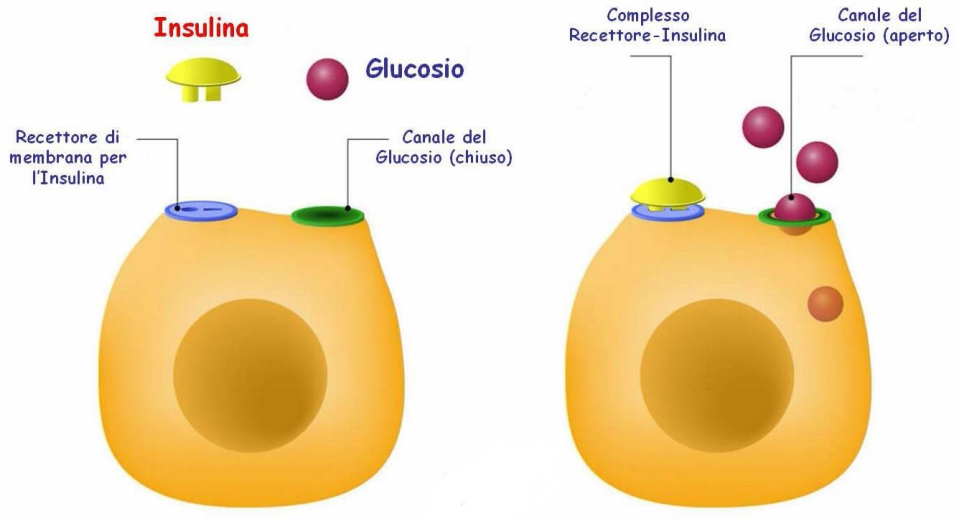

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Format: Abstract

Send to

Ann N Y Acad Sci. 2019 May 14. doi: 10.1111/nyas.14107. [Epub ahead of print]

Gut microbiome and its role in obesity and insulin resistance.

Lee CJ[1,2], Sears CL[3,4], Maruthur N[2,5,6].

Author information

Ruolo microbioma nella Obesità e Resistenza insulinica

Abstract

Obesity is a complex metabolic disease caused, in part, by the interaction between an individual's genetics, metabolism, and environment. Emerging evidence supports the role of gut microbiota in mediating the interaction between the host and environment by extracting energy from food otherwise indigestible by the host and producing metabolites and cytokines that affect host metabolism. Furthermore, gut microbial imbalance or dysbiosis has been shown in metabolic diseases including obesity, and recent studies are beginning to unravel the mechanisms involved. The gut microbiota affects host metabolism and obesity through several pathways involving gut barrier integrity, production of metabolites affecting satiety and insulin resistance, epigenetic factors, and metabolism of bile acids and subsequent changes in metabolic signaling. While the field of gut microbiome and its role in obesity is early in its stage of development, it holds a promising future in providing us with novel therapeutic targets that may restore the gut microbiome to a healthy state and help in the prevention and treatment of obesity.

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https://www.ncbi.nlm.nih.gov/pubmed/31087391

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Journal List > J Ovarian Res > v.13; 2020 > PMC7301991

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Journal of Ovarian Research
BMC

J Ovarian Res. 2020; 13: 73.
Published online 2020 Jun 17. doi: 10.1186/s13048-020-00670-3

PMCID: PMC7301991
PMID: 32552864

Role of gut microbiota in the development of insulin resistance and the mechanism underlying polycystic ovary syndrome: a review

Fang-fang He and Yu-mei Li

Author information · Article notes · Copyright and License information Disclaimer

Update
Ruolo microbioma nella Resistenza insulinica e PCOS

Abstract

Go to:

Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder. Typically, it is characterized by hirsutism, hyperandrogenism, ovulatory dysfunction, menstrual disorders and infertility. To date, its pathogenesis remains unclear. However, insulin resistance (IR) is considered as the primary pathological basis for its reproductive dysfunction. On the other hand, a condition in which insulin is over-secreted is called hyperinsulinemia. IR/Hyperinsulinemia is associated with chronic inflammation, hormonal changes, follicular dysplasia, endometrial receptivity changes, and abortion or infertility. Additionally, it increases incidence of complications during pregnancy and has been associated with anxiety, depression, and other psychological disorders. Gut microbiota, the "second genome" acquired by the human body, can promote metabolism, immune response through interaction with the external environment. Gut microbiota dysbiosis can cause IR, which is closely linked to the occurrence of PCOS. This article reviewed recent findings on the roles of gut microbiota in the development of insulin resistance and the mechanism underlying polycystic ovary syndrome.

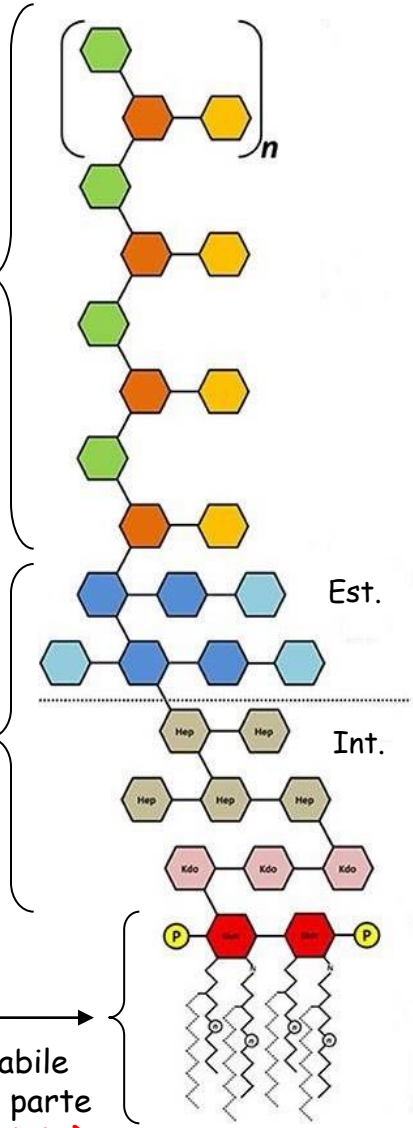
J Ovarian Res

Mauro Amato

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7301991/

Lipopolisaccaridi (LPS)

- Componenti parete batteri gram- (enterobatteri)
- **Endotossine** o Lipoglicani
- **Antigene O** (somatico) **Core** **Lipide A**



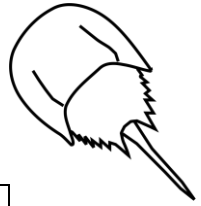
oligosacaride

Responsabile della gran parte della **tossicità batterica**

Laboratorio

Limulus Test Limulus Amoebocyte Lysate (**LAL**)
Test Cromogenico
Test Immunoturbidimetrico
Immunochimico (**ELISA** LPS specifico)

Presenza nel lisato di amebociti di **Limulus Poliphemus** di un proenzima che attivato da LPS determina la **gelificazione del lisato** stesso



Disbiosi

Basato sulla **reazione anticorpo** (anti-LPS presente in ambiente di reazione) **e antigene** (LPS presenti nel campione) con sviluppo e misura della **torbidità** proporzionale alla quantità di LPS

Sviluppo **colore** in seguito all'**attivazione** del **proenzima Factor C** da parte del LAL. Intensità del colore proporzionale alla quantità di LPS presenti nei liquidi biologici.
Test aspecifico

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Chapter 8

Detection Methods for Lipopolysaccharides: Past and Present

Loreen R. Stromberg, Heather M. Mendez and Harshini Mukundan

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.68311

Metodi per determinazione Lipopolisaccaridi

https://www.intechopen.com/books/-i-escherichia-coli-i-recent-advances-on-physiology-pathogenesis-and-biotechnological-applications/detection-methods-for-lipopolysaccharides-past-and-present

Abstract

Lipopolysaccharide (LPS) is the primary component of the outer membrane of Gram-negative bacteria. LPS aids in protecting bacterial cells, and also defines the unique serogroups used to classify bacteria. Additionally, LPS is an endotoxin and the primary stimulator of innate immune cells in mammals, making it an ideal candidate for early detection of pathogens. However, the majority of methods for detection of LPS focus on detection of the endotoxic component of the molecule, lipid A. Since lipid A is largely conserved among bacterial species and serogroups, these detection approaches are highly nonspecific. Thus, the importance of identifying the O-polysaccharide antigenic portion of LPS, which confers serogroup specificity, has received a great deal of attention in recent years. However, methods that are highly selective to the O-antigens are typically less sensitive than those that target the endotoxin. Here we present a history and comparison of the sensitivity of these methods and their value for detecting bacteria in a variety of different sample types.

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Journal List > Am J Pathol > v.182(2); 2013 Feb > PMC3562736

The American Journal of PATHOLOGY
Cellular and Molecular Biology of Disease
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Am J Pathol. 2013 Feb; 182(2): 375–387.
doi: 10.1016/j.ajpath.2012.10.014

PMCID: PMC3562736
PMID: 23201091

Lipopolysaccharide Causes an Increase in Intestinal Tight Junction Permeability *in Vitro* and *in Vivo* by Inducing Enterocyte Membrane Expression and Localization of TLR-4 and CD14

Shuhong Guo,*† Rana Al-Sadi,*† Hamid M. Said,‡ and Thomas Y. Ma*†*

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This article has been cited by other articles in PMC.

Abstract

Go to:

Bacterial-derived lipopolysaccharides (LPS) play an essential role in the inflammatory process of inflammatory bowel disease. A defective intestinal tight junction (TJ) barrier is an important pathogenic factor of inflammatory bowel disease and other inflammatory conditions of the gut. Despite its importance in mediating intestinal inflammation, the physiological effects of LPS on the intestinal epithelial barrier remain unclear. The major aims of this study were to determine the effects of physiologically relevant concentrations of LPS (0 to 1 ng/mL) on intestinal barrier function using an *in vitro* (filter-grown Caco-2 monolayers) and an *in vivo* (mouse intestinal perfusion) intestinal epithelial model system. LPS, at physiologically relevant concentrations (0 to 1 ng/mL), in the basolateral compartment produced a time-dependent increase in Caco-2 TJ permeability without inducing cell death. Intraperitoneal injection of LPS (0.1 mg/kg), leading to clinically relevant plasma concentrations, also caused a time-dependent increase in intestinal permeability *in vivo*. The LPS-induced increase in intestinal TJ permeability was mediated by an increase in enterocyte membrane TLR-4 expression and a TLR-4–dependent increase in membrane colocalization of membrane-associated protein CD14. In conclusion, these studies show for the first time that LPS causes an increase in intestinal permeability via an intracellular mechanism involving TLR-4–dependent up-regulation of CD14 membrane expression.

Correlazione diretta LPS/Leaky Gut

Mauro Amato

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3562736/

JAHA
Journal of the American Heart Association

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Gut-Derived Serum Lipopolysaccharide is Associated With Enhanced Risk of Major Adverse Cardiovascular Events in Atrial Fibrillation: Effect of Adherence to Mediterranean Diet

Daniele Pastori, Roberto Carnevale, Cristina Nocella, Marta Novo, Maria Santulli, Vittoria Cammisotto, Danilo Menichelli, Pasquale Pignatelli, and Francesco Violi

Originally published 5 Jun 2017 | https://doi.org/10.1161/JAHA.117.005784 | Journal of the American Heart Association. :6:e005784

Jump to

Abstract
Introduction
Methods
Results
Discussion
Disclosures
Footnotes
References

Associazione diretta LPS/Fibrillazione atriale

Associazione inversa Dieta mediterranea/LPS

Abstract

Background

Gut microbiota is emerging as a novel risk factor for atherothrombosis, but the predictive role of gut-derived lipopolysaccharide (LPS) is unknown. We analyzed (1) the association between LPS and major adverse cardiovascular events (MACE) in atrial fibrillation (AF) and (2) its relationship with adherence to a Mediterranean diet (Med-diet).

Methods and Results

This was a prospective single-center study including 912 AF patients treated with vitamin K antagonists (3716 patient-years). The primary end point was a composite of MACE. Baseline serum LPS, adherence to Med-diet (n=704), and urinary excretion of 11-dehydro-thromboxane B_2 (TxB_2, n=852) were investigated. Mean age was 73.5 years; 42.9% were women. A total of 187 MACE (5.0% per year) occurred: 54, 59, and 74 in the first, second, and third tertile of LPS, respectively (log-rank test P=0.004). Log-LPS (hazard ratio 1.194, P=0.009), age (hazard ratio 1.083, P<0.001), and previous cerebrovascular (hazard ratio 1.634, P=0.004) and cardiac events (hazard ratio 1.822, P<0.001) were predictors of MACE. In the whole cohort, AF (versus sinus rhythm) (β 0.087, P=0.014) and low-density lipoprotein cholesterol (β 0.069, P=0.049) were associated with circulating LPS. Furthermore, Med-diet score (β −0.137, P<0.001) was predictive of log-LPS, with fruits (β −0.083, P=0.030) and legumes (β −0.120, P=0.002) negatively associated with log-LPS levels. Log-LPS and log-TxB_2 were highly correlated (r=0.598, P<0.001). Log-LPS (β 0.574, P<0.001) and Med-diet score (β −0.218, P<0.001) were significantly associated with baseline urinary excretion of TxB_2.

Conclusions

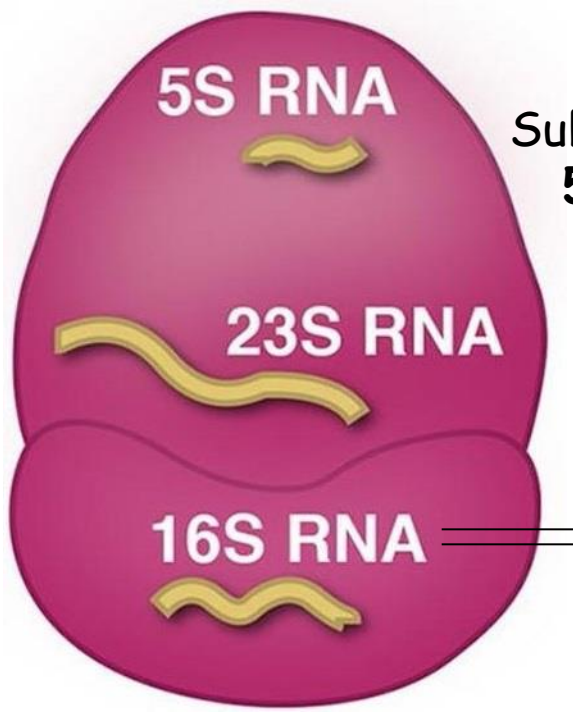
In this cohort of AF patients, LPS levels were predictive of MACE and negatively affected by high adherence to Med-diet. LPS may contribute to MACE incidence in AF by increasing platelet activation.

Mauro Amato

https://www.ahajournals.org/doi/full/10.1161/JAHA.117.005784

Identificazione MICROBIOTA
16S rRNA gene sequencing

Ribosoma batterico
70S



Subunità
50S

Subunità
30S

Studio Gene codificante 16S rRNA

↓

informazioni tassonomiche

- **Geni 16S rRNA sono un misto di zone ipervariabili** e **zone conservate**
- Studiando zone diverse dello stesso gene si ottengono informazioni a diverso livello tassonomico

Amplificazione PCR

Geni molto conservati	Zone geniche ipervariabili	Regioni spaziatrici	Zone random nel genoma
↓	↓	↓	↓
Genere	**Specie**	**Sottospecie**	**Ceppo**

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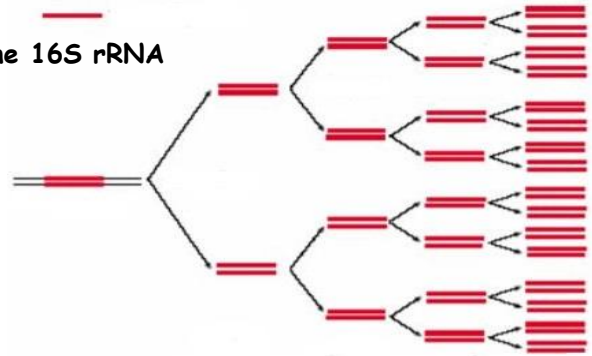
Identificazione MICROBIOTA
16S rRNA gene sequencing

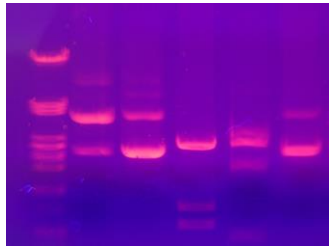
Campione feci

Estrazione del DNA



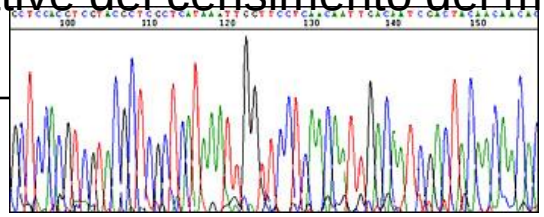
Amplificazione PCR

dalle analisi descrittive del censimento del microbiota agli studi di causa ed effetto



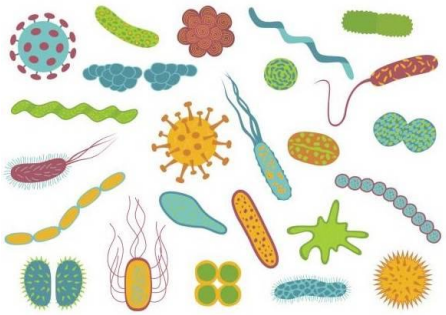
Separazione DNA
elettroforesi su gel di agarosio

Purificazione
16S rRNA



Sequenziamento DNA

DNA Data Bank



Identificazione

Fotografia istantanea legata al **solo momento del prelievo fecale.**
La ricerca tende a spostarsi **dalle analisi del censimento allo studio causa/effetto sulla fisiologia dell'ospite**

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nature reviews microbiology

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Review Article | Published: 04 September 2020

Gut microbiota in human metabolic health and disease

Yong Fan & Oluf Pedersen

Nature Reviews Microbiology (2020) | Cite this article

6706 Accesses | 198 Altmetric | Metrics

Studio causa/effetto della alterazione microbiota sulla fisiologia dell'ospite viene preferita al censimento del microbiota stesso

Come il microbiota e suoi metaboliti possono collegarsi al metabolismo dell'ospite sano o alla patogenesi di malattie metaboliche

Abstract

Observational findings achieved during the past two decades suggest that the intestinal microbiota may contribute to the metabolic health of the human host and, when aberrant, to the pathogenesis of various common metabolic disorders including obesity, type 2 diabetes, non-alcoholic liver disease, cardio-metabolic diseases and malnutrition. However, to gain a mechanistic understanding of how the gut microbiota affects host metabolism, research is moving from descriptive microbiota census analyses to cause-and-effect studies. Joint analyses of high-throughput human multi-omics data, including metagenomics and metabolomics data, together with measures of host physiology and mechanistic experiments in humans, animals and cells hold potential as initial steps in the identification of potential molecular mechanisms behind reported associations. In this Review, we discuss the current knowledge on how gut microbiota and derived microbial compounds may link to metabolism of the healthy host or to the pathogenesis of common metabolic diseases. We highlight examples of microbiota-targeted interventions aiming to optimize metabolic health, and we provide perspectives for future basic and translational investigations within the nascent and promising research field.

https://www.nature.com/articles/s41579-020-0433-9

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PMC Advanced Journal list

Journal List > Microorganisms > v.7(1); 2019 Jan > PMC6351938

Enpab webinar

microorganisms MDPI

Microorganisms. 2019 Jan; 7(1): 14.
Published online 2019 Jan 10. doi: 10.3390/microorganisms7010014

PMCID: PMC6351938
PMID: 30634578

What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases

Emanuele Rinninella,[1,2,*] Pauline Raoul,[2] Marco Cintoni,[3] Francesco Franceschi,[4,5] Giacinto Abele Donato Miggiano,[1,2] Antonio Gasbarrini,[2,6] and Maria Cristina Mele[1,2]

Author information Article notes Copyright and License information Disclaimer

Composizione Microbiota in funzione della dieta, età, ambiente e malattie

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https://www.ncbi.nlm.nih.gov/pubmed/30634578

Abstract

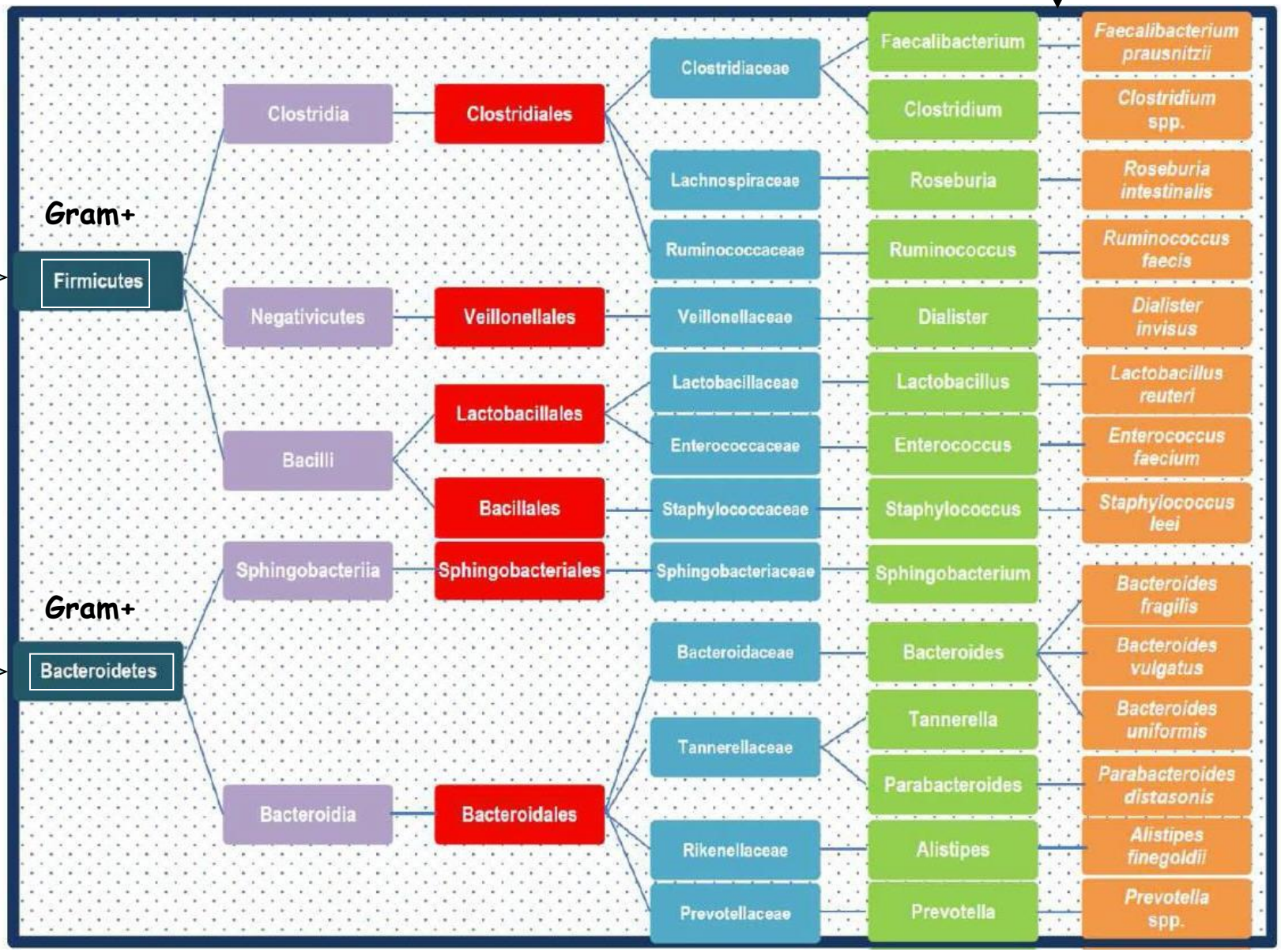
Go to:

Each individual is provided with a unique gut microbiota profile that plays many specific functions in host nutrient metabolism, maintenance of structural integrity of the gut mucosal barrier, immunomodulation, and protection against pathogens. Gut microbiota are composed of different bacteria species taxonomically classified by genus, family, order, and phyla. Each human's gut microbiota are shaped in early life as their composition depends on infant transitions (birth gestational date, type of delivery, methods of milk feeding, weaning period) and external factors such as antibiotic use. These personal and healthy core native microbiota remain relatively stable in adulthood but differ between individuals due to enterotypes, body mass index (BMI) level, exercise frequency, lifestyle, and cultural and dietary habits. Accordingly, there is not a unique optimal gut microbiota composition since it is different for each individual. However, a healthy host–microorganism balance must be respected in order to optimally perform metabolic and immune functions and prevent disease development. This review will provide an overview of the studies that focus on gut microbiota balances in the same individual and between individuals and highlight the close mutualistic relationship between gut microbiota variations and diseases. Indeed, dysbiosis of gut microbiota is associated not only with intestinal disorders but also with numerous extra-intestinal diseases such as metabolic and neurological disorders. Understanding the cause or consequence of these gut microbiota balances in health and disease and how to maintain or restore a healthy gut microbiota composition should be useful in developing promising therapeutic interventions.

Mauro Amato

Microorganisms **2019**, *7*, 14

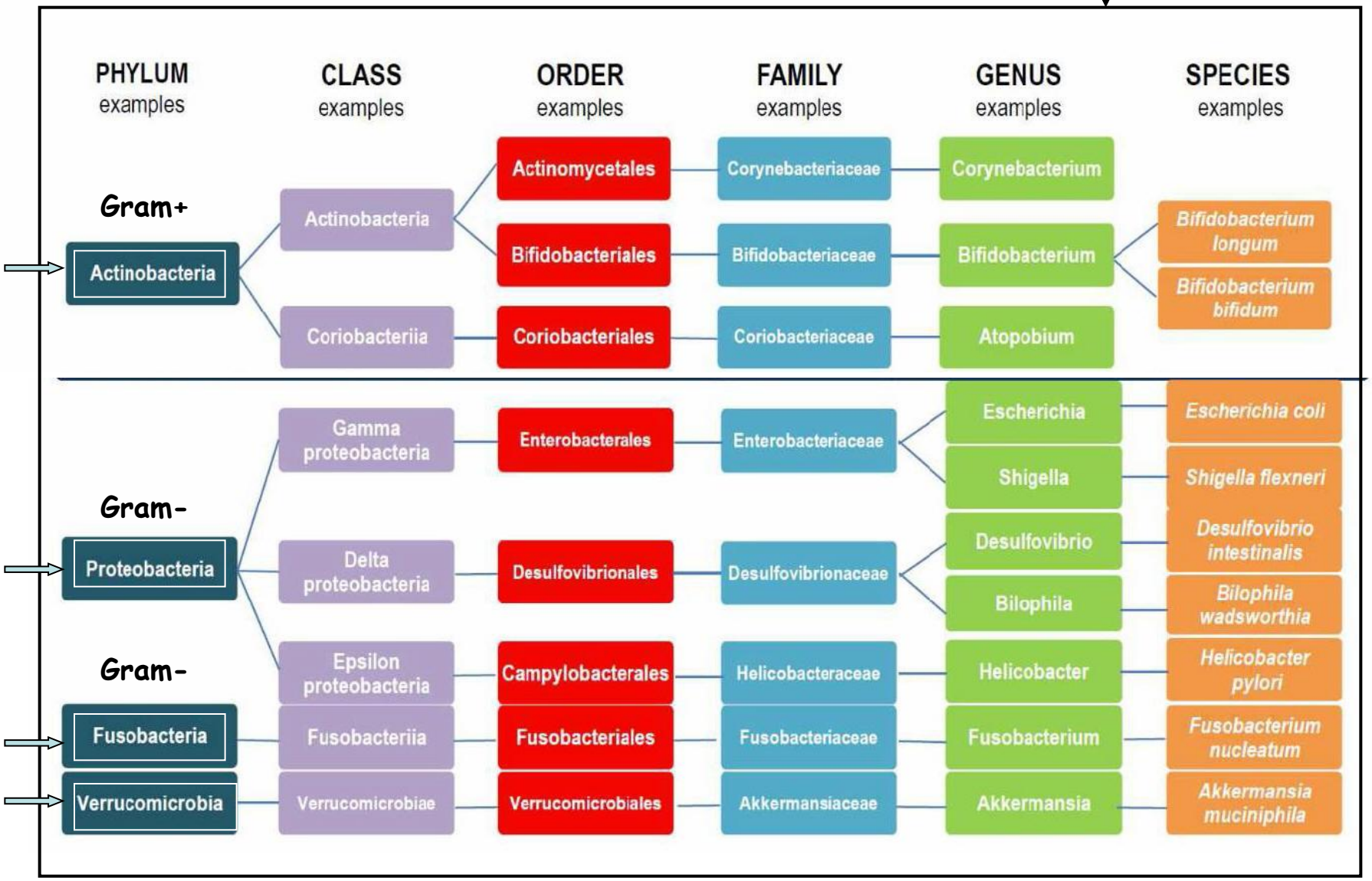
MICROBIOTA Intestinale — 90%



Mauro Amato

Microorganisms **2019**, *7*, 14

MICROBIOTA Intestinale — 10%



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Nature Microbiology

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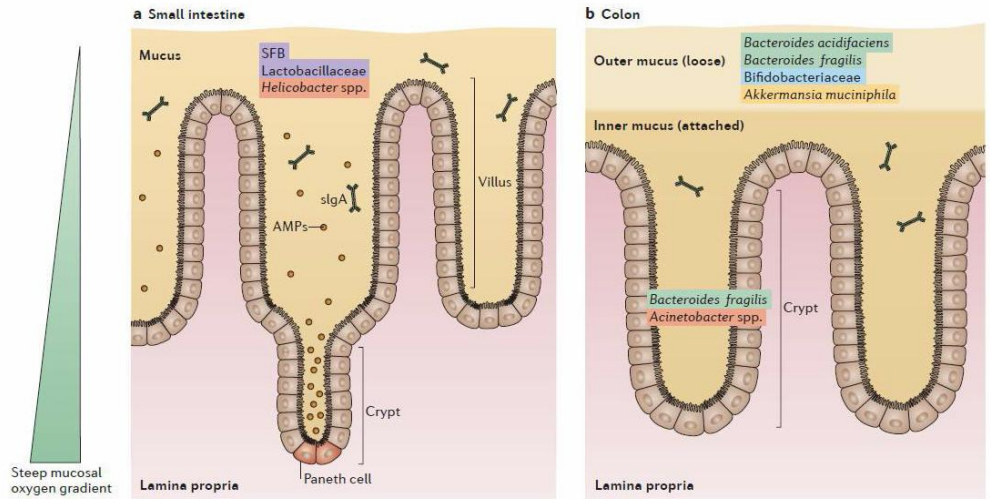


MICROBIOME

Gut biogeography of the bacterial microbiota

Gregory P. Donaldson, S. Melanie Lee and Sarkis K. Mazmanian

Abstract | Animals assemble and maintain a diverse but host-specific gut microbial community. In addition to characteristic microbial compositions along the longitudinal axis of the intestines, discrete bacterial communities form in microhabitats, such as the gut lumen, colonic mucus layers and colonic crypts. In this Review, we examine how the spatial distribution of symbiotic bacteria among physical niches in the gut affects the development and maintenance of a resilient microbial ecosystem. We consider novel hypotheses for how nutrient selection, immune activation and other mechanisms control the biogeography of bacteria in the gut, and we discuss the relevance of this spatial heterogeneity to health and disease.

Biogeografia microbiota intestinale

Mauro Amato

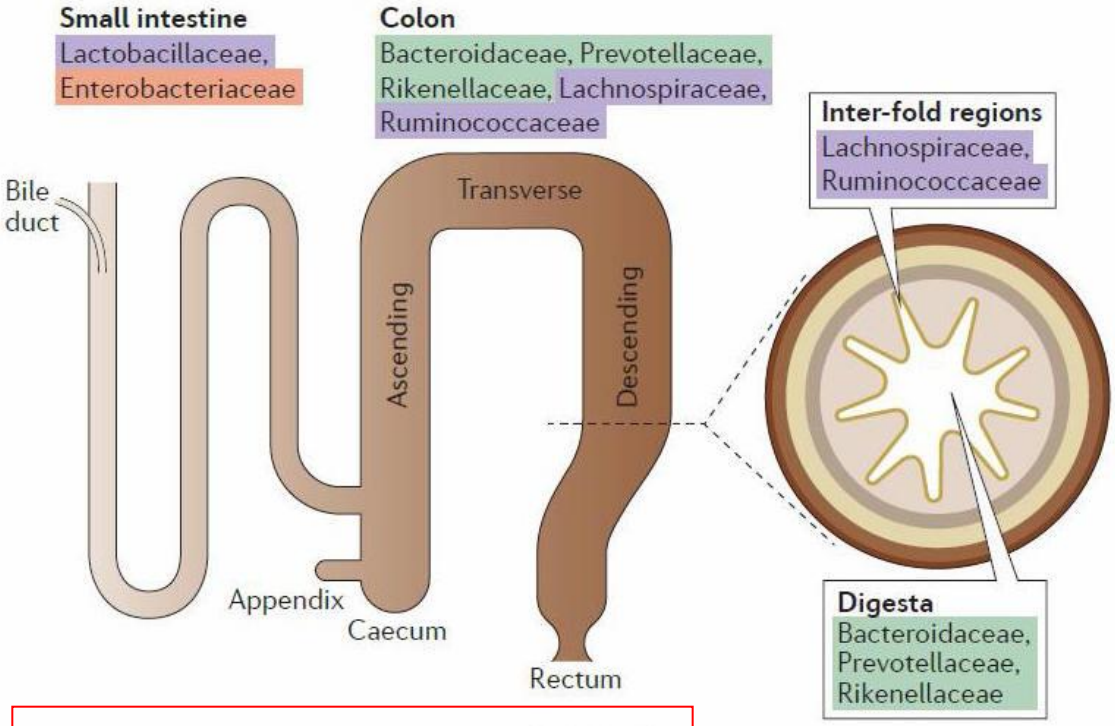
https://www.researchgate.net/publication/283264463_Gut_biogeography_of_the_bacterial_microbiota

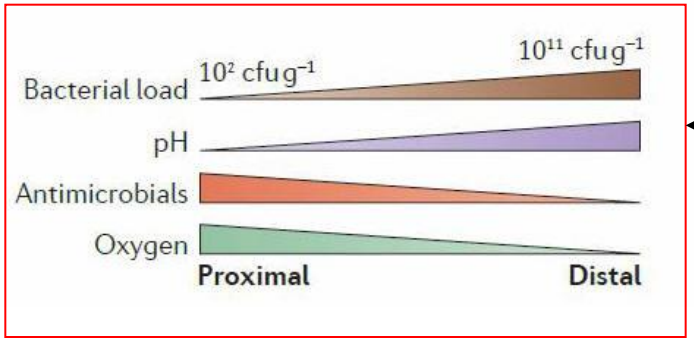
MICROBIOTA Intestinale

Dominant gut phyla:

Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Verrucomicrobia

Predominant families in the:





Le famiglie batteriche riflettono differenze fisiologiche lungo l'intestino in funzione della carica batterica, del pH, delle sostanze antimicrobiche (compresi i secreti biliari) e del tenore di O2

www.nature.com/micro

Mauro Amato

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Advanced Journal list

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Journal List › Front Endocrinol (Lausanne) › v.10; 2019 › PMC6363653

frontiers in Endocrinology

Front Endocrinol (Lausanne). 2019; 10: 29.
Published online 2019 Jan 30. doi: 10.3389/fendo.2019.00029

PMCID: PMC6363653
PMID: 30761090

Impact of Gut Microbiota on Host Glycemic Control

Céline Gérard and Hubert Vidal*

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Firmicuti/Bacteroiditi e target glicemico ottimale dell'ospite

This article has been cited by other articles in PMC.

Abstract

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6363653/

Go to:

Given that obesity and associated disorder type II diabetes mellitus have reached epidemic proportions worldwide, the development of efficient prevention and therapeutic interventions is a global public health interest. There is now a large body of evidence suggesting that the micro-organisms colonizing the human gut, known as gut microbiota, play a central role in human physiology and metabolism. Understanding how gut microbiota affects and regulates key metabolic functions such as glucose regulation and insulin resistance is an important health issue. The present review summarizes recent advances in our understanding of how gut bacterial species interfere with host metabolic phenotype. We will examine key biological molecular mechanisms underlying the impact of gut microbiota on host glycemic control including: incretin secretion, short-chain fatty acid production, bile acid metabolism, and adipose tissue regulation. We will highlight how prebiotic/probiotic interventions affect these bacterial processes and are now considered as promising approaches to treat obese and diabetic patients.

Front Endocrinol (Lausanne)

Front End

Mauro Amato

Sono numerose le **malattie/sindromi** in qualche modo **collegate alla Disbiosi intestinale**
Le più studiate:

↓

Gastrointestinali: **MICI**, **IBS**, Cancro colon-retto, Infezione da Clostridium difficile

Malattie croniche: Morbo di Alzheimer e di Parkinson, Disordini Spettro Autistico, Sindrome da stanchezza cronica

Malattie autoimmuni: Artrite reumatoide, Sclerosi multipla, DMT1

Metabolismo: Obesità, Sindrome metabolica, DMT2

Mauro Mario Amato
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Disease categories	Specific diseases	Associated dysbiotic features
Immune-mediated/autoimmune diseases	inflammatory bowel disease (IBD)	• Increase in virulent gut microbes (*Enterobacteriaceae* species, *Bacteroides fragilis*) and mucolytic *Ruminococcus* sp. • Decrease in butyrate-producing *Firmicutes* (such as *Faecalibacterium prausnitzii*, *Roseburia hominis*)
	Irritable bowel syndrome (IBS)	• Increase in *Escherichia coli* • Decrease in *Clostridium leptum* group of bacteria and *Bifidobacterium*. • Decrease in bile acid biotransformation
	Celiac disease	• Increase in *Bacteroides–Prevotella* group • Decrease in *Bifidobacterium* • Varying observation (decrease or no change) in *Clostridium histolyticum*, *C. lituseburense*, and *Faecalibacterium prausnitzii* • Alteration in SCFAs composition, but overall increase in total SCFA
	Systemic lupus erythematosus (SLE)	• Increase in *Blautia* sp. and Gram-negative bacteria such as *Proteobacteria*. • Decrease in gut microbiota diversity, *Odoribacter* sp., *Alistipes* sp. • Increase in serum endotoxin
	Type-1 diabetes	• Increase in *Bacteroidetes* • Decrease in *Actinobacteria*, *Firmicutes*, and *Firmicutes/Bacteroidetes* ratio
	Rheumatoid arthritis (RA)	• Increase in *Prevotella copri* and decrease in *Bacteroides* sp. In new-onset RA • Increase in microbiota diversity of *Lactobacillus* genus in early RA
	Atopic disease (E.g., childhood allergic asthma)	• Increase in fecal burden of *Clostridium difficile*, and *C. difficile/Bifidobacteria* ratio
Metabolic disorders/cardiovascular disorders	Obesity	• Increase in *Firmicutes*, *Actinobacter* • Varying observation (decrease, no change, increase) in *Bacteroidetes* • Increase in glycoside hydrolase and SCFAs (butyrate and acetate)
	Type-2 diabetes	• Increase in *Lactobacillus* • Decrease in *Clostridium coccoides*, *Atopobium* cluster, and *Prevotella* • Decrease in butyrate biosynthesis
	Hypertension	• Increase in the Firmicutes/Bacteroidetes ratio, lactate-producer • Decrease in microbiota diversity, acetate- and butyrate-producers
	Atherosclerosis	• Increase in metabolites TMAO, endotoxin level (risk factor for early atherosclerosis)
Cancer	Colorectal cancer (CRC)	• Increase in enterotoxigenic *Bacteroides fragilis*, and pathobionts *Fusobacterium* and *Campylobacter* sp. • Decrease in butyrate-producer (*Faecalibacterium* and *Roseburia*)
Neurop sy chi atri c	Autism spectrum disorder (ASD)	• Increase in *Clostridium* sp., *Bacteroidetes*, *Lactobacillus*, *Desulfovibrio* • Decrease in *Bifidobacteria*
	Alzheimer's disease	• Possible connection between gut microbiota-synthesized amyloids, LPS, γ-aminobutyric acid (GAB A – major inhibitory neurotransmitter), and the increased permeability of gut barrier and blood brain barrier with age
	Depression	• Increase in genus *Eggerthella*, *Holdemania*, *Gelria*, *Turicibacter*, *Paraprevotella*, *Anaerofilum* • Decrease in gut microbiota diversity, *Prevotella* and *Dialister*
	Parkinson's Disease	• Increase in anti-inflammatory butyrate-producers from genus *Blautia*, *Coprococcus*, and *Roseburia* in patient fecal sample, pro-inflammatory *Proteobacteria* in patient mucosa • Increased gene expression in LPS biosynthesis and microbial type III secretion system
Infectious disease	*Clostridium difficile* infection (CDI)	• Increase in *Clostridium difficile*; • Decrease in gut microbiota diversity and secondary bile acids-producing *Clostridium scindens*
Uremic disease	Chronic kidney disease	• Increase in *Firmicutes*, *Proteobacteria*, and *Actinobacteria* • Decrease in *Lactobacilli*

Frontiers in Microbiology

August 2018 | Volume 9 | Article 1835

The Human Gut Microbiome
A Potential Controller of Wellness and Disease

Tipo di Disbiosi/Specificità di malattia

Enpab webinar

Mauro Amato

Disease/ disorder	Implicated microbiota	Potential role of the microbiome
IMMUNE DISEASES		
IBD	Bacteroidetes *Lachnospiraceae* *Actinobacteria* *Proteobacteria* *Clostridium leptum* *Clostridium coccoides* *Faecalibacterium prausnitzii* Firmicutes/Bacteroidetes ratio *Bifidobacteria*	Immune response to the gut microbial community Composition of the gut microbiota contributes to inflammation
Allergies	*Lactobacillus* spp. *Bifidobacterium adolescentis* *Clostridium difficile*	Early colonization with *Lactobacillus* is associated with decreased allergies Early colonization with more diverse microbiota might prevent allergies
Celiac disease	*Bacteroides vulgatus* *Escherichia coli* *Clostridium coccoides*	High diversity in Celiac disease patients vs. control
Type I diabetes	*Bacteroides* *Streptococci* *Clostridium cluster IV and XIVa*	Interaction between the gut community and the innate immune system may be a predisposing factor for diabetes
Rheumatoid arthritis	Bifidobacteria *Bacteroides* *Porphyromonas* *Prevotella* *Bacteroides fragilis* *Eubacterium rectale* *Clostridium coccoides*	Treg-promoting organisms depleted; overgrowth of bacteria that induce Th17 cell populations, leading to inflammation Intestinal microbes associated with etiology
Atopy and asthma	Bifidobacteria *Bacteroides* *Staphylococcus* spp. *Streptococcus* spp. Enterobacteria *Clostridium difficile*	Pre- and post-natal microbial exposure appear key to appropriate immune development Mode of delivery and nutrient uptake are important factors for GI community development and protection against subsequent atopic disease development

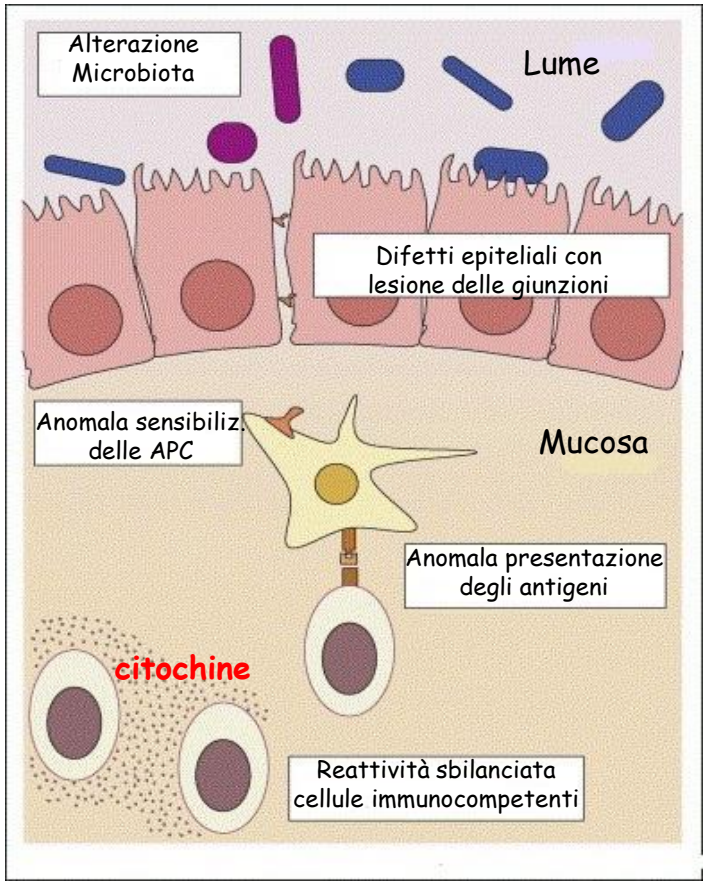
Disease/ disorder	Implicated microbiota	Potential role of the microbiome
METABOLIC DISEASES		
Obesity	Firmicutes/Bacteroidetes ratio Prevotellaceae Eubacterium Faecalibacterium Roseburia	Significant changes in gut microbiota are associated with increased obesity
Type II diabetes	Bacteroidetes/Firmicutes Bacteroides-Prevotella *Eggerthella lenta* *Clostridia* *Eubacterium rectale* *Faecalibacterium prausnitzii* *Roseburia intestinalis* *Roseburia inulinivorans*	Shifts in gut microbiota are associated with increases in plasma glucose concentrations
Hypertension	*Prevotella* *Klebsiella* *Bifidobacterium* *Butyrivibrio* *Coprococcus* *Faecalibacterium* *Roseburia*	Gut dysbiosis increases hypertension
AUTISM		
Autism	*Clostridial species*	Increased bacterial diversity in the feces of autistic children compared to control
PSYCHOLOGICAL DISEASE		
Anxiety and depression	*Lactobacillus reuteri* *Lactobacillus rhamnosus* *Bifidobacterium infantis*	Decreased anxiety and stress-induced increase of corticosterone

Specificità di Malattia/Microbiota implicato

Mauro Amato

https://www.frontiersin.org/articles/10.3389/fmicb.2018.01510/full

DISBIOSI e IBD/MICI (Malattie Infiammatorie Croniche Intestinali)



laboratorio

Fattori Ambientali

Stress psicologico
Fumo di sigaretta (Crohn)
Appendicectomia

Dieta e stato sociale
Farmaci
Contraccezione orale

Alterazione Microbiota Leaky Gut → metaboliti → **MICI** ← citochine ← **Immunità compromessa**

Predisposizione Genetica → **MICI**

Si associano:
- Emocromocitometrico, sideremia, ferritina
- Ricerca sangue occulto e leucociti fecali
- Test di permeabilità intestinale (Zonulina)
- Determinazione Tossina A/B Clostridium diff.
- a1-Antitripsina
- Viro-immunologia: HBV, HCV, HIV, EBV, CMV
- Coprocoltura e parassitologico feci
- Zinco e Magnesio
- Vit. B12, Acido Folico

Test di I livello
- VES, PCR e ß2-Microglobulina
- Calprotectina e Lactoferrina fecale
- Anticorpi anti-citoplasma dei neutrofili (ANCA)
- Anticorpi anti-Saccharomyces Cerevisiae (ASCA)

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Format: Abstract

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Clin J Gastroenterol. 2018 Feb;11(1):1-10. doi: 10.1007/s12328-017-0813-5. Epub 2017 Dec 29.

Gut microbiota in the pathogenesis of inflammatory bowel disease.

Ruolo microbiota nella patogenesi MICI

Nishida A[1], Inoue R[2], Inatomi O[3], Bamba S[3], Naito Y[4], Andoh A[3].

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4 Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto, 602-8566, Japan.

Abstract

Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, is a chronic and relapsing inflammatory disorder of the intestine. Although its incidence is increasing globally, the precise etiology remains unclear and a cure for IBD has yet to be discovered. The most accepted hypothesis of IBD pathogenesis is that complex interactions between genetics, environmental factors, and the host immune system lead to aberrant immune responses and chronic intestinal inflammation. The human gut harbors a complex and abundant aggregation of microbes, collectively referred to as the gut microbiota. The gut microbiota has physiological functions associated with nutrition, the immune system, and defense of the host. Recent advances in next-generation sequencing technology have identified alteration of the composition and function of the gut microbiota, which is referred to as dysbiosis, in IBD. Clinical and experimental data suggest dysbiosis may play a pivotal role in the pathogenesis of IBD. This review is focused on the physiological function of the gut microbiota and the association between the gut microbiota and pathogenesis in IBD. In addition, we review the therapeutic options for manipulating the altered gut microbiota, such as probiotics and fecal microbiota transplantation.

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https://www.ncbi.nlm.nih.gov/pubmed/29285689

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Journal List › Diseases › v.8(2); 2020 Jun › PMC7348996

diseases MDPI

Diseases. 2020 Jun; 8(2): 13.
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PMCID: PMC7348996
PMID: 32397606

Inflammatory Bowel Diseases: Host-Microbial-Environmental Interactions in Dysbiosis

Catherine Colquhoun, Michelle Duncan, and George Grant*

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Abstract

Go to:

Crohn's Disease (CD) and Ulcerative Colitis (UC) are world-wide health problems in which intestinal dysbiosis or adverse functional changes in the microbiome are causative or exacerbating factors. The reduced abundance and diversity of the microbiome may be a result of a lack of exposure to vital commensal microbes or overexposure to competitive pathobionts during early life. Alternatively, many commensal bacteria may not find a suitable intestinal niche or fail to proliferate or function in a protective/competitive manner if they do colonize. Bacteria express a range of factors, such as fimbriae, flagella, and secretory compounds that enable them to attach to the gut, modulate metabolism, and outcompete other species. However, the host also releases factors, such as secretory IgA, antimicrobial factors, hormones, and mucins, which can prevent or regulate bacterial interactions with the gut or disable the bacterium. The delicate balance between these competing host and bacteria factors dictates whether a bacterium can colonize, proliferate or function in the intestine. Impaired functioning of NOD2 in Paneth cells and disrupted colonic mucus production are exacerbating features of CD and UC, respectively, that contribute to dysbiosis. This review evaluates the roles of these and other the host, bacterial and environmental factors in inflammatory bowel diseases.

Enpab webinar

Interazioni Microbiota/Ambiente nella patogenesi MICI

Mauro Amato

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7348996/

frontiers in Medicine

ORIGINAL RESEARCH
published: 20 November 2018
doi: 10.3389/fmed.2018.00304

Enpab webinar

Disease-Specific Enteric Microbiome Dysbiosis in Inflammatory Bowel Disease

Hengameh Chloé Mirsepasi-Lauridsen[1], Katleen Vrankx[2], Jørgen Engberg[3], Alice Friis-Møller[4], Jørn Brynskov[5], Inge Nordgaard-Lassen[6], Andreas Munk Petersen[4,6] and Karen Angeliki Krogfelt[1]*

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Diversità Microbiota durante gli stadi attivi/inattivi del CD e UC

OPEN ACCESS

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Inflammatory Bowel disease (IBD) is traditionally divided into Crohn's disease (CD) and ulcerative colitis (UC). UC is a relapsing non-transmural inflammatory disease that is restricted to the colon and is characterized by flare-ups of bloody diarrhea. CD is a chronic, segmental localized granulomatous disease that can affect any part of the entire gastrointestinal tract. Ileo-anal pouch is a procedure restoring functionality of the rectum after a colectomy. IBD is a multifactorial disease and flares of IBD are probably triggered by changes in the intestinal microbiota followed by an abnormal immune response. In this study, we aim to analyze the intestinal bacterial diversity in IBD patients during various stages of disease compared with healthy controls. Permission for human experiments and recruitment of participants was obtained from the Ethic Committee for Copenhagen County hospitals (Permission no. KA-03019, Permission no. KA-20060159). Stools from 26 healthy controls, 42 CD, 38 UC and 18 pouch patients were collected. Stool DNA extraction was performed using Qiagen, DNA mini stool kit Denmark. DGGE-PCR amplifying the V2-V3 region of 16S-rDNA gene of the bacteria was amplified by universal primers HDA1 and HDA2. Analysis of DGGE was performed blinded using BioNumerics version 7.5. After normalization, a DGGE gel band matching was performed. The similarities between profiles were calculated with a ranked Pearson correlation coefficient based on the band matching results using band intensities. Simpson's index of diversity and Pielou's species evenness were calculated. Based on the Shannon Diversity Index, UC patients had lower species diversity and bacterial evenness in comparison to healthy persons, $p < 0.05$. However, only CD and disease pouch patients had lower species diversity compared to those with inactive disease and healthy controls. Well-functioning pouch patients had decreased species evenness in comparison to diseased pouch patients and control group. During the active disease stage in CD and pouch, the patients have a low bacterial diversity in their gut when compared to the inactive stage. In UC patients, a generally low diversity was observed at all stages of the disease compared to healthy controls.

Mauro Amato

https://www.frontiersin.org/articles/10.3389/fmed.2018.00304/full

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Curr Pharm Des. 2020;26(25):2951-2961. doi: 10.2174/1381612826666200420144128.

Inflammatory Bowel Diseases: The Role of Gut Microbiota

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Affiliations – collapse

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PMID: 32310042 DOI: 10.2174/1381612826666200420144128

Update sul Microbiota
Somministrazione pre/probiotici
Trapianto Microbiota fecale
nelle MICI

Abstract

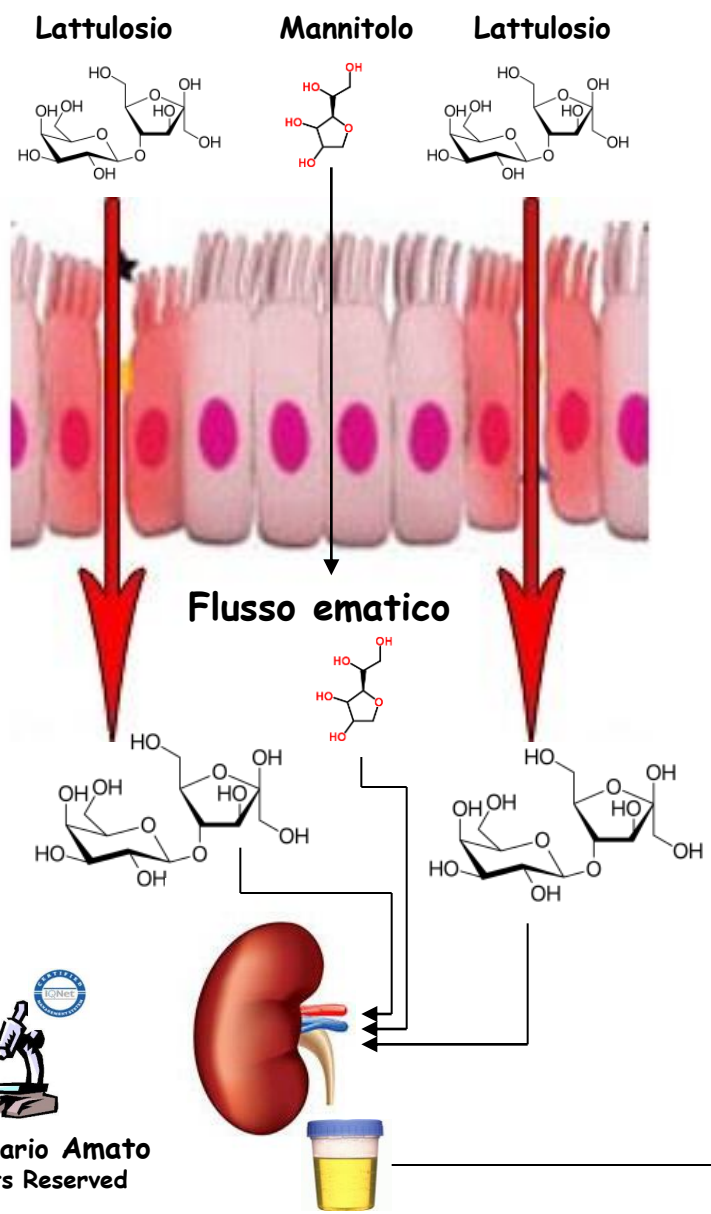
Inflammatory bowel diseases (IBD) are chronic multifactorial diseases characterized by partially unclear pathogenic mechanisms including changes in intestinal microbiota. Despite the microbiota, alteration is well established in IBD patients, as reported by 16RNA sequencing analysis, an important goal is to define if it is just a consequence of the disease progression or a trigger factor of the disease itself. To date, gut microbiota composition and gut microbiota-related metabolites seem to affect the host healthy state both by modulating metabolic pathways or acting on the expression of different genes through epigenetic effects. Because of this, it has been suggested that intestinal microbiota might represent a promising therapeutic target for IBD patients. The aim of this review is to summarize both the most recent acquisitions in the field of gut microbiota and its involvement in intestinal inflammation together with the available strategies for the modulation of microbiota, such as prebiotics and/or probiotics administration or fecal microbiota transplantation.

Mauro Amato

https://pubmed.ncbi.nlm.nih.gov/32310042/

DISBIOSI

TEST DI PERMEABILITA' INTESTINALE
(Rapporto Lattulosio/Mannitolo)



- **Test diretto** più comune **per una Leaky Gut**: Utilizza il **Lattulosio** come grossa molecola e il **Mannitolo** come piccola.
  Normalmente il **Lattulosio** viene **assorbito** soltanto per l'**1%** mentre il **Mannitolo** per circa il **14%**
- Essendo **zuccheri non metabolizzabili** si ritroveranno **escreti nelle urine**.

- Dopo aver fatto osservare alcune precauzioni, al paziente vengono somministrati 5 gr. di Lattulosio e 1 gr. di Mannitolo.
- Dopo **6 ore** si dosano, in un campione di urine dello stesso paziente, questi due composti.

Il **rapporto Lattulosio/Mannitolo deve essere inferiore a 0.03** (in un intestino sano passeranno nel flusso ematico e saranno escrete solo le molecole più piccole di mannitolo).

- La presenza di molecole di Lattulosio (più grandi) nelle urine è indicativa di **Aumentata Permeabilità Intestinale**

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PERMEABILITA' INTESTINALE
Tight Junction e Zonulina

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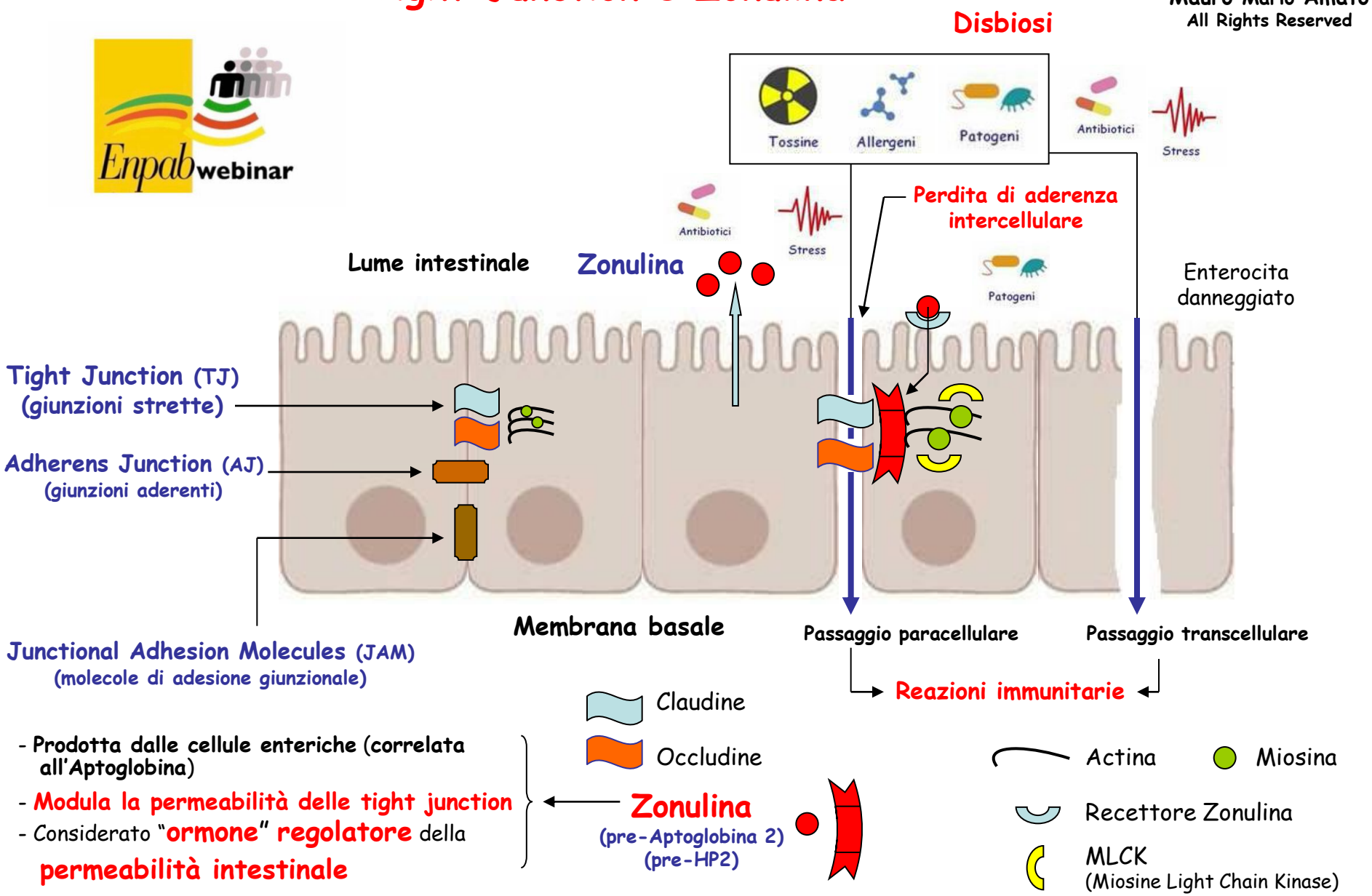
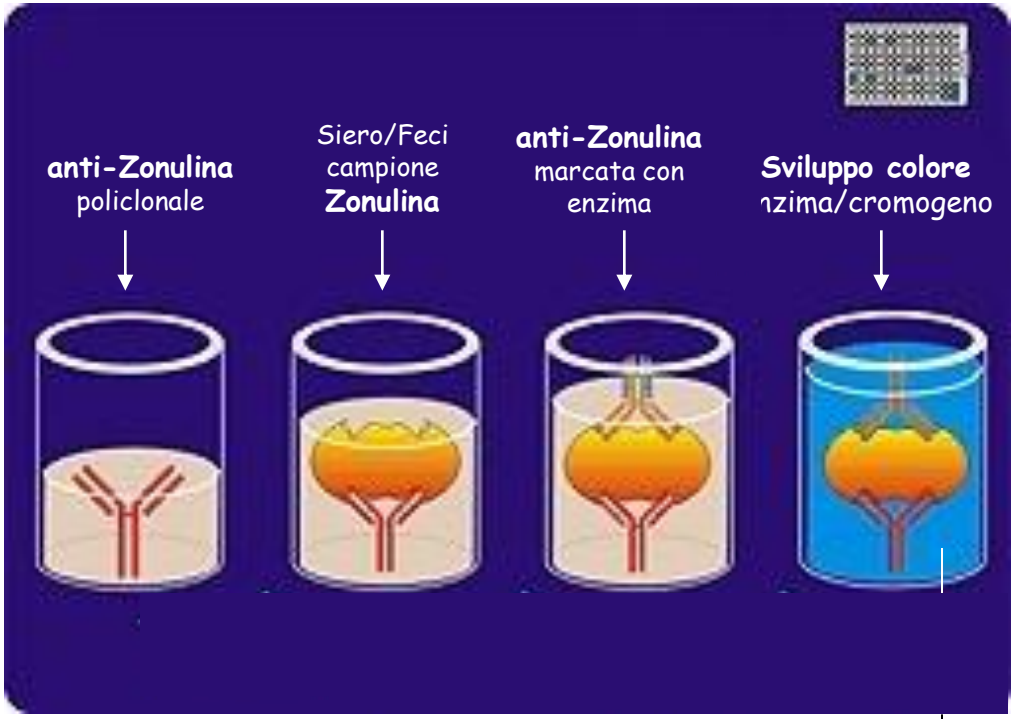


- Prodotta dalle cellule enteriche (correlata all'Aptoglobina)
- Modula la permeabilità delle tight junction
- Considerato "ormone" regolatore della permeabilità intestinale

ZONULINA —— Immunoenzimatico ELISA



Intensità di colore proporzionale alla concentrazione della Zonulina

Valori riferimento

14-108 ng/ml
su campione di feci

< 38.0 ng/ml
su campione **siero/plasma**

Valori aumentati di zonulina indicano una leaky gut più o meno evidente in relazione alla concentrazione di zonulina nelle siero/feci

- Sensazione di gonfiore addominale
- Crampi addominali
- Stitichezza/Diarrea

E' stato evidenziato che la **zonulina** sierica o **aumentata**:

- **Celiachia**
- **Malattie autoimmuni**
- **Sindrome metabolica**
- **Diabete 2 e PCOS**
- **Obesità e Iperlipemia**
- **Depressione e autismo**
- **Declino cognitivo**

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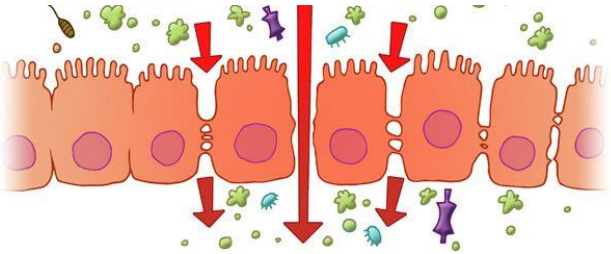
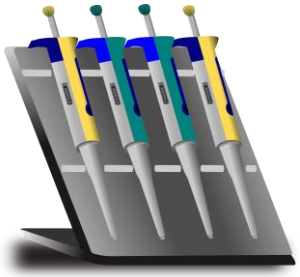
Biomarcatori di Leaky Gut

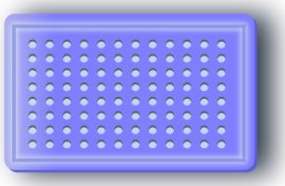


- **Zonulina** **sierica**/fecale
- **I-FABP** (Intestinal Fatty Acid Binding Protein) plasma/urine
- **IL-6** (Interleuchina 6) plasma/siero

Immunochimica/ELISA → In condizioni normali non è rilevabile

Immunochimica/Elettrochemiluminescenza ultra-sensibile → fino a **1.8** pg/mL





Enpab webinar

Mauro Mario Amato
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Reviews

Zonulin, a regulator of epithelial and endothelial bar functions, and its involvement in chronic inflammato diseases

Craig Sturgeon & Alessio Fasano

Article: e1251384 | Received 20 Sep 2016, Accepted 14 Oct 2016, Accepted author version posted online: 21 Oct 2016, Published online: 10 Nov 2016

Download citation https://doi.org/10.1080/21688370.2016.1251384 Check for updates

Full Article | Figures & data | References | Citations | Metrics | Reprints & Permissions | PDF

ABSTRACT

Coinvolgimento della zonulina nelle MICI

Beside digesting nutrients and absorbing solutes and electrolytes, the intestinal epithelium with its barrier function is in charge of a tightly controlled antigen trafficking from the intestinal lumen to the submucosa. This trafficking dictates the delicate balance between tolerance and immune response causing inflammation. Loss of barrier function secondary to upregulation of zonulin, the only known physiological modulator of intercellular tight junctions, leads to uncontrolled influx of dietary and microbial antigens. Additional insights on zonulin mechanism of action and the recent appreciation of the role that altered intestinal permeability can play in the development and progression of chronic inflammatory disorders has increased interest of both basic scientists and clinicians on the potential role of zonulin in the pathogenesis of these diseases.

https://www.tandfonline.com/doi/full/10.1080/21688370.2016.1251384

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Journal List > F1000Res > v.9; 2020 > PMC6996528

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Version 1. F1000Res. 2020; 9: F1000 Faculty Rev-69.
Published online 2020 Jan 31. doi: 10.12688/f1000research.20510.1

PMCID: PMC6996528
PMID: 32051759

All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases

Alessio Fasano, Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Resources, Visualization, Writing – Original Draft Preparation[a,1,2]

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Abstract

Go to:

Improved hygiene leading to reduced exposure to microorganisms has been implicated as one possible cause for the recent "epidemic" of chronic inflammatory diseases (CIDs) in industrialized countries. That is the essence of the hygiene hypothesis that argues that rising incidence of CIDs may be, at least in part, the result of lifestyle and environmental changes that have made us too "clean" for our own good, so causing changes in our microbiota. Apart from genetic makeup and exposure to environmental triggers, inappropriate increase in intestinal permeability (which may be influenced by the composition of the gut microbiota), a "hyper-belligerent" immune system responsible for the tolerance–immune response balance, and the composition of gut microbiome and its epigenetic influence on the host genomic expression have been identified as three additional elements in causing CIDs. During the past decade, a growing number of publications have focused on human genetics, the gut microbiome, and proteomics, suggesting that loss of mucosal barrier function, particularly in the gastrointestinal tract, may substantially affect antigen trafficking, ultimately influencing the close bidirectional interaction between gut microbiome and our immune system. This cross-talk is highly influential in shaping the host gut immune system function and ultimately shifting genetic predisposition to clinical outcome. This observation led to a re-visitation of the possible causes of CIDs epidemics, suggesting a key pathogenic role of gut permeability. Pre-clinical and clinical studies have shown that the zonulin family, a group of proteins modulating gut permeability, is implicated in a variety of CIDs, including autoimmune, infective, metabolic, and tumoral diseases. These data offer novel therapeutic targets for a variety of CIDs in which the zonulin pathway is implicated in their pathogenesis.

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La permeabilità intestinale legata a tutte le malattie?

Permeabilità zonulina-mediata nella patogenesi delle MICI

Mauro Amato

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6996528/

Enpab webinar

REVIEW

Tissue Barriers 1:5, e27321; 2013; © 2013 Landes Bioscience

The role of Haptoglobin and its related protein, Zonulin, in inflammatory bowel disease

Tim Vanuytsel, Séverine Vermeire and Isabelle Cleynen*

Department of Clinical and Experimental Medicine; TARGID; KU Leuven

Keywords: crohn's disease, haptoglobin, inflammatory bowel disease, intestinal barrier, intestinal permeability, ulcerative colitis, zonulin

Aptoglobila/Zonulina
Ruolo nelle MICI

Crohn's disease (CD) and ulcerative colitis (UC), collectively called inflammatory bowel disease (IBD), are immune-mediated conditions characterized by a chronic inflammation of the gut. Their precise etiology is unknown, although an increased intestinal permeability has been shown to play a central role in the pathogenesis of IBD. The intestinal epithelium provides the largest interface between the external environment and the host, and is thus a crucial regulation site of innate and adaptive immunity. Zonulin is one of the few known physiological mediators of paracellular intestinal permeability. It was found upregulated in different immune diseases like Celiac disease and Type 1 Diabetes (T1D). Recently, human zonulin was identified as prehaptoglobin-2 (pre-HP2) which before only had been regarded as the inactive precursor for HP2. Haptoglobin (HP) is a hemoglobin-binding protein with immunomodulatory properties. Its gene harbors a common polymorphism with 2 different alleles: *HP1* and *HP2*. Allele *HP2* and genotype *HP22* has been shown to be overrepresented in different immune diseases like Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE) and T1D, and has also been found to be more frequent in patients with IBD (UC and CD) than in healthy controls.

In order to get some clues about the mechanism of action of HP(2) in IBD pathogenesis, we here review the current state of knowledge about zonulin and haptoglobin structure and function, and their plausible role in immune mediated diseases with an emphasis on IBD.

of specific transporters, passive flux of small water-soluble solutes and ions occurs mainly via the paracellular route, which is controlled by the apical junctional complex.[2,3] Tight junctions, the principal part of the junctional complex, are composed of transmembrane proteins of which occludin and the claudins are the best characterized, and peripheral membrane proteins like zonula-occludens 1 (ZO-1) which link the transmembrane tight junction-related proteins to the perijunctional cytoskeleton.[4-6] Initially regarded as static intercellular sealing structures, tight junctions are increasingly recognized as flexible gatekeepers regulating the flow across the epithelium.[7]

An abnormal barrier function, as reflected by increased intestinal permeability, has been implicated in a variety of conditions like Celiac disease and Type 1 Diabetes.[8-10] An increased intestinal permeability has also been shown to play a central role in the pathogenesis of Crohn's disease (CD) and ulcerative colitis (UC), jointly called inflammatory bowel disease (IBD).[11-16] IBD is a chronic, relapsing, inflammatory disorder of the gastrointestinal tract. It is a complex and polygenic disease that affects an increasing number of people in Western countries and more recently also in Asia.[17,18] The current accepted hypothesis for its pathogenesis is that a dysregulated immune response occurs to the commensal microbiota in the gut in a genetically susceptible subject.[19,20] It is thus plausible that an impaired intestinal epithelial barrier allows for the interaction between an unprocessed antigen and the mucosal immune sys-

https://www.tandfonline.com/doi/pdf/10.4161/tisb.27321?needAccess=true

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Journal List > Nat Commun > PMC7181728

nature COMMUNICATIONS

Nat Commun. 2020; 11: 1995.
Published online 2020 Apr 24. doi: 10.1038/s41467-020-15831-7

PMCID: PMC7181728
PMID: 32332732

Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis

Narges Tajik,[#1,2] Michael Frech,[#1,2] Oscar Schulz,[1,2] Fabian Schälter,[1,2] Sébastien Lucas,[1,2] Vugar Azizov,[1,2] Kerstin Dürholz,[1,2] Franziska Steffen,[1,2] Yasunori Omata,[1,2] Andreas Rings,[3] Marko Bertog,[4] Aroldo Rizzo,[5] Aida Iljazovic,[6] Marijana Basic,[7] Arnd Kleyer,[1,2] Stephan Culemann,[1,2] Gerhard Krönke,[1,2] Yubin Luo,[8] Klaus Überla,[2,9] Udo S. Gaipl,[10] Benjamin Frey,[10] Till Strowig,[6] Kerstin Sarter,[1,2] Stephan C. Bischoff,[3] Stefan Wirtz,[2,11] Juan D. Cañete,[12] Francesco Ciccia,[5] Georg Schett,[1,2] and Mario M. Zaiss[✉1,2]

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Approccio preventivo sulla Artrite (malattie autoimmuni) studiando la permeabilità zonulina-mediata

Abstract

Go to:

Gut microbial dysbiosis is associated with the development of autoimmune disease, but the mechanisms by which microbial dysbiosis affects the transition from asymptomatic autoimmunity to inflammatory disease are incompletely characterized. Here, we identify intestinal barrier integrity as an important checkpoint in translating autoimmunity to inflammation. Zonulin family peptide (zonulin), a potent regulator for intestinal tight junctions, is highly expressed in autoimmune mice and humans and can be used to predict transition from autoimmunity to inflammatory arthritis. Increased serum zonulin levels are accompanied by a leaky intestinal barrier, dysbiosis and inflammation. Restoration of the intestinal barrier in the pre-phase of arthritis using butyrate or a cannabinoid type 1 receptor agonist inhibits the development of arthritis. Moreover, treatment with the zonulin antagonist larazotide acetate, which specifically increases intestinal barrier integrity, effectively reduces arthritis onset. These data identify a preventive approach for the onset of autoimmune disease by specifically targeting impaired intestinal barrier function.

Nat Commun

Nat Commun

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7181728/

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Journal List > Int J Mol Sci > v.18(3); 2017 Mar > PMC5372598

International Journal of Molecular Sciences MDPI

Int J Mol Sci. 2017 Mar; 18(3): 582.
Published online 2017 Mar 8. doi: 10.3390/ijms18030582

PMCID: PMC5372598
PMID: 28282855

Higher Levels of Serum Zonulin May Rather Be Associated with Increased Risk of Obesity and Hyperlipidemia, Than with Gastrointestinal Symptoms or Disease Manifestations

Bodil Ohlsson,[1,*] Marju Orho-Melander,[2,†] and Peter M. Nilsson[1,†]

Sabrina Angelini, Academic Editor

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[2]Genetic Epidemiology, Diabetes and Cardiovascular Disease, Lund University, 205 02 Malmö, Sweden; marju.orho-melander@med.lu.se
[*]Correspondence: bodil.ohlsson@med.lu.se; Tel.: +46-4033-2323
[†]These authors contributed equally to this work.

This article has been cited by other articles in PMC.

Abstract

Go to:

Zonulin is considered a biomarker of increased intestinal permeability, and elevated levels have been found

Associazione diretta tra Zonulina serica e Iperlididemia/Obesità

Mauro Amato

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5372598/

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Randomized Controlled Trial

J Dairy Sci. 2020 May;103(5):3961-3970.

doi: 10.3168/jds.2019-17696. Epub 2020 Mar 12.

Effects of kefir or milk supplementation on zonulin in overweight subjects

Z Jenko Pražnikar [1], S Kenig [1], T Vardjan [2], M Černelič Bizjak [1], A Petelin [3]

Affiliations + expand

PMID: 32171508 DOI: 10.3168/jds.2019-17696

Miglioramento dei marcatori di permeabilità intestinale con Kefir nei sovrappeso

Abstract

Increased intestinal permeability has been shown to be involved in several diseases associated with low-grade chronic inflammation, including obesity and metabolic syndrome. In the last decade, growing evidence shows the beneficial effects of probiotic-containing food supplementation on these conditions. In this crossover intervention study on 28 asymptomatic overweight adults, we tested the effects of a 3-wk kefir supplementation compared with a 3-wk milk supplementation on serum zonulin levels. The effects on serum glucose, triacylglycerols, low-density lipoproteins, high-density lipoproteins, total cholesterol, markers of inflammation (C-reactive protein and adiponectin), anthropometric variables, mood, and appetite were also determined. Kefir supplementation resulted in a greater improvement of serum zonulin levels ($F = 6.812$, $\eta^2 = 0.275$), whereas a significant yet similar improvement in lipid profile and serum glucose levels was found in both supplementations. Positive mood was slightly but significantly enhanced with kefir supplementation, and reduced with milk supplementation. The C-reactive protein, adiponectin, and appetite were unaffected. In conclusion, supplementation with both dairy products had health beneficial effects, but only kefir showed an effect on the intestinal barrier dysfunction marker.

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JCRPE Journal of Clinical Research in Pediatric Endocrinology HOME

J Clin Res Pediatr Endocrinol. 2017 Mar; 9(1): 31–38.
Published online 2017 Mar 1. doi: 10.4274/jcrpe.3682

PMCID: PMC5363162
PMID: 28008865

The Relationship between Serum Zonulin Level and Clinical and Laboratory Parameters of Childhood Obesity

Tuncay Küme,[1] Sezer Acar,[2] Hale Tuhan,[2] Gönül Çatlı,[2] Ahmet Anık,[2] Özlem Gürsoy Çalan,[1] Ece Böber,[2] and Ayhan Abacı[2,*]

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This article has been corrected. See J Clin Res Pediatr Endocrinol. 2020 September; 12(3): 331.

This article has been cited by other articles in PMC.

Abstract

Go to:

Objective:

To investigate the relationship between zonulin levels and clinical and laboratory parameters of childhood obesity.

Methods:

The study included obese children with a body mass index (BMI) >95th percentile and healthy children who were of similar age and gender distribution. Clinical (BMI, waist circumferences, mid-arm circumference, triceps skinfold, percentage of body fat, systolic blood pressure, diastolic blood pressure) and biochemical (glucose, insulin, lipid levels, thyroid function tests, cortisol, zonulin and leptin levels) parameters were measured.

Results:

A total of 43 obese subjects (23 males, mean age: 11.1±3.1 years) and 37 healthy subjects (18 males, mean age: 11.5±3.5 years) were included in this study. Obese children had significantly higher insulin, homeostasis model assessment of insulin resistance, triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), zonulin and leptin levels than healthy children ($p<0.05$), while glucose levels were not different ($p>0.05$). Comparison of the obese children with and without insulin resistance showed no statistically significant differences for zonulin levels ($p>0.05$). Zonulin levels were found to negatively correlate with HDL-C and positively correlate with leptin levels, after adjusting for age and BMI.

Zonulina significativamente elevata nella obesità infantile

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5363162/

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Mol Cell Biochem. 2014 Mar;388(1-2):203-10. doi: 10.1007/s11010-013-1911-4. Epub 2013 Dec 18.

Increased circulatory levels of lipopolysaccharide (LPS) and zonulin signify novel biomarkers of proinflammation in patients with type 2 diabetes.

Jayashree B[1], Bibin YS, Prabhu D, Shanthirani CS, Gokulakrishnan K, Lakshmi BS, Mohan V, Balasubramanyam M.

Author information

LPS e Zonulina quali Biomarcatori di proinfiammazione DMT2 → **Associazione diretta LPS e Zonulina serica e Infiammazione/DMT2**

Abstract

Emerging data indicate that gut-derived endotoxin (metabolic endotoxemia) may contribute to low-grade systemic inflammation in insulin-resistant states. Specific gut bacteria seem to serve as lipopolysaccharide (LPS) sources and several reports claim a role for increased intestinal permeability in the genesis of metabolic disorders. Therefore, we investigated the serum levels of LPS and zonulin (ZO-1, a marker of gut permeability) along with systemic levels of tumor necrosis factor-α (TNF-α) and Interleukin-6 (IL-6) in patients with type 2 diabetes mellitus (T2DM) compared to control subjects. Study subjects were recruited from the Chennai Urban Rural Epidemiology Study [CURES], Chennai, India. Study group (n = 45 each) comprised of a) subjects with normal glucose tolerance (NGT) and (b) patients with T2DM. LPS, ZO-1, TNF-α, and IL-6 levels were measured by ELISA. Serum levels of LPS [$p < 0.05$], LPS activity [$p < 0.001$], ZO-1 [$p < 0.001$], TNFα [$p < 0.001$], and IL-6 [$p < 0.001$] were significantly increased in patients with T2DM compared to control subjects. Pearson correlation analysis revealed that LPS activity was significantly and positively correlated with ZO-1, fasting plasma glucose, 2 h post glucose, HbA1c, serum triglycerides, TNF-α, IL-6, and negatively correlated with HDL cholesterol. Regression analysis showed that increased LPS levels were significantly associated with type 2 diabetes [odds ratio (OR) 13.43, 95 % CI 1.998-18.9; $p = 0.003$]. In Asian Indians who are considered highly insulin resistant, the circulatory LPS levels, LPS activity, and ZO-1 were significantly increased in patients with type 2 diabetes and showed positive correlation with inflammatory markers and poor glycemic/lipid control.

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https://www.ncbi.nlm.nih.gov/pubmed/24347174

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Eur J Endocrinol. 2015 Jan;172(1):29-36. doi: 10.1530/EJE-14-0589. Epub 2014 Oct 21.

Serum zonulin is elevated in women with polycystic ovary syndrome and correlates with insulin resistance and severity of anovulation.

Zhang D[1], Zhang L[2], Yue F[2], Zheng Y[2], Russell R[2].

Author information

Associazione diretta
Zonulina serica/PCOS

Abstract

OBJECTIVE: Evidence suggests that increased gut permeability may be associated with polycystic ovary syndrome (PCOS). Human zonulin is currently the only physiological mediator known to reversibly regulate gut permeability by disassembling intestinal tight junctions. So far, no data on serum zonulin levels in patients with PCOS are available. This study aimed to determine circulating serum zonulin levels in women with PCOS and discuss the relationship between zonulin, insulin resistance, and menstrual disorders in this group.

DESIGN: A case-control study.

METHODS: The study includes 78 women recently diagnosed with PCOS and 63 age-matched healthy controls recruited. Serum zonulin levels were determined by ELISA. Insulin resistance was assessed by homeostasis model assessment of insulin resistance (HOMA-IR) and Matsuda and DeFronzo's insulin sensitivity index (ISI).

RESULTS: PCOS women had higher serum zonulin levels ($P=0.022$). After adjustment for age and BMI, zonulin levels significantly correlated with HOMA-IR and ISI. Furthermore, PCOS women with more severe menstrual disorders had significantly higher zonulin levels and displayed an inverse correlation between zonulin and the number of menstrual cycles per year ($r=-0.398$, $P<0.001$).

CONCLUSIONS: Serum zonulin, a biomarker for gut permeability, is increased in PCOS women and correlates with insulin resistance and severity of menstrual disorders. It suggests that alterations in gut permeability may play a role in the pathophysiology of PCOS, and serum zonulin might be used as a biomarker for both risk stratification and therapeutic outcomes in PCOS women.

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https://www.ncbi.nlm.nih.gov/pubmed/25336505

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DIALOGO INTESTINO-CERVELLO E PERMEABIITA' INTESTINALLE

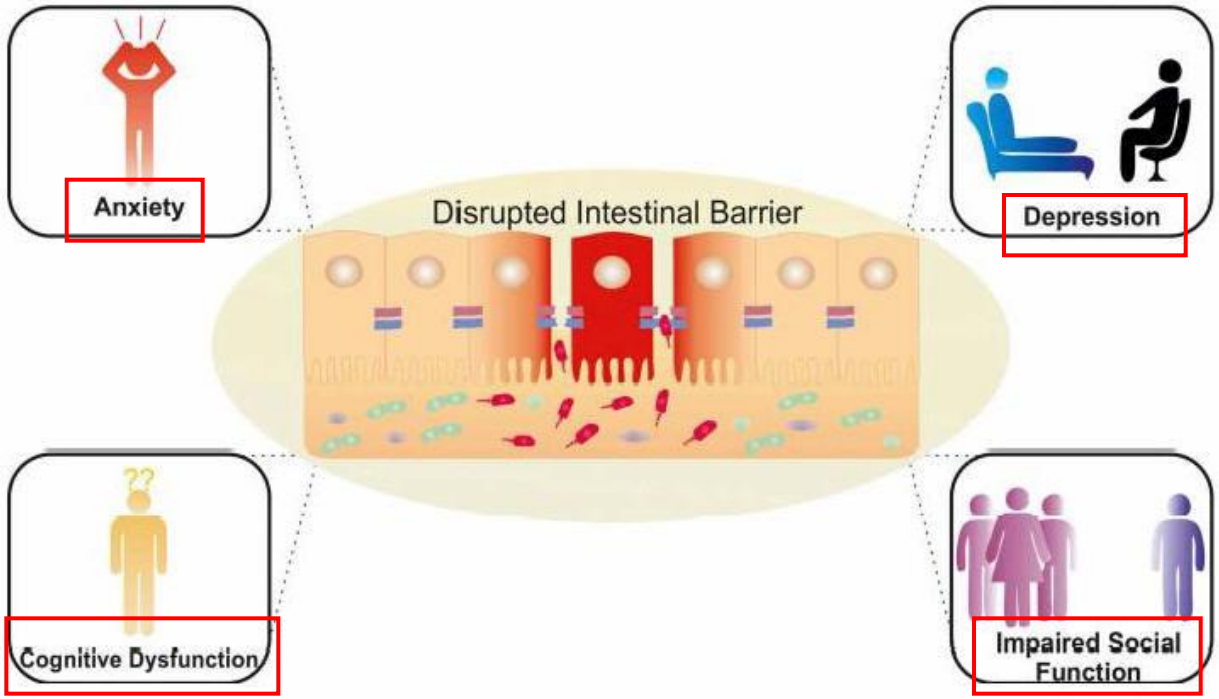

FIGURE 2 | Potential neuropsychiatric consequences of a dysregulated intestinal barrier. Activation of brain-gut-microbiota Axis signaling pathways via a compromised intestinal barrier with potential effects on mood, anxiety, cognition and social interaction.

Conseguenze neuropsichiatriche correlate all'aumentata permeabilità intestinale

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Frontiers in Cellular Neuroscience 10.3389/fncel.2015.00392

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Acta Psychiatr Scand. 2019 Feb; 139(2): 185–193.
Published online 2018 Nov 1. doi: 10.1111/acps.12978

PMCID: PMC6587489
PMID: 30347427

Leaky gut biomarkers in depression and suicidal behavior

L. Ohlsson,[1] A. Gustafsson,[1] E. Lavant,[1] K. Suneson,[2] L. Brundin,[3] Å. Westrin,[2] L. Ljunggren,[1,†] and D. Lindqvist[⊠2,†]

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E-mail: daniel.lindqvist@med.lu.se
†These authors contributed equally to this work.

Abstract

Go to:

Objective

Inflammation is associated with major depressive disorder (MDD) and suicidal behavior. According to the 'leaky gut hypothesis', increased intestinal permeability may contribute to this relationship via bacterial translocation across enterocytes. We measured plasma levels of gut permeability markers, in patients with a recent suicide attempt (rSA), MDD subjects with no history of a suicide attempt (nsMDD), and healthy controls (HC), and related these markers to symptom severity and inflammation.

Associazione
Aumentata Permeabilità intestinale
Depressione e Comportamento suicidario

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6587489/

Mauro Amato

SINDROME DELL'INTESTINO IRRITABILE (IBS) – Criteri diagnostici Consensus Roma IV

Dolore addominale recidivante, in media, almeno 1 giorno alla settimana negli ultimi 3 mesi, associato a 2 o più delle seguenti caratteristiche:

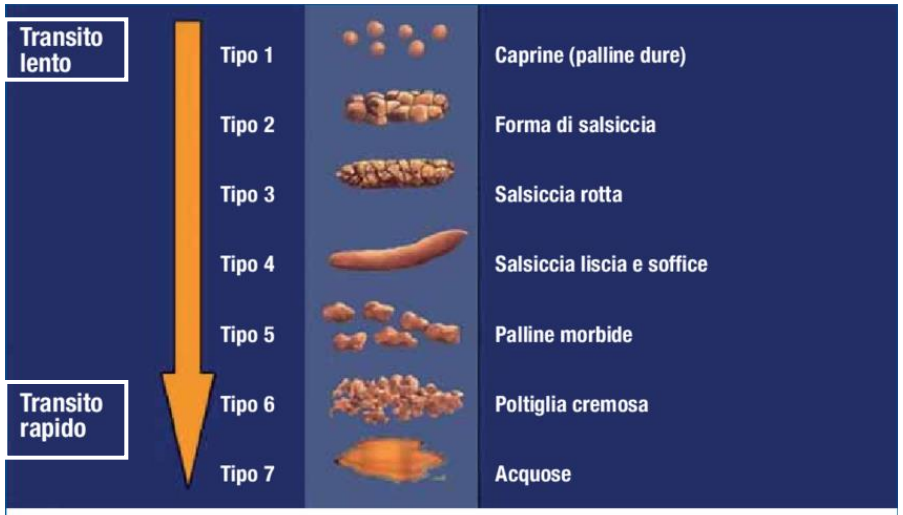
- associato alla defecazione
- associato a modificazioni della frequenza delle evacuazioni
- associato a modificazioni della forma/consistenza delle evacuazioni

tali criteri devono essere rispettati negli ultimi 3 mesi ed essere iniziati da almeno 6 mesi

Tabella I: Criteri diagnostici di sindrome dell'intestino irritabile di Roma IV

- IBS-STIPSI PREVALENTE IBS-C: presenza di feci dure o caprine >25% delle evacuazioni, presenza di feci non formate <25% delle evacuazioni
- IBS-DIARREA PREVALENTE IBS-D: presenza di feci non formate >25% delle evacuazioni, presenza di feci dure o caprine <25% delle evacuazioni
- IBS-ALVO MISTO IBS-M: presenza di feci non formate >25% delle evacuazioni e presenza di feci dure o caprine >25% delle evacuazioni
- IBS-Non –SPECIFICATA IBS-U: criteri insufficienti per caratterizzare la IBS come stipsi prevalente, diarrea prevalente o alvo misto

Tabella II: Sottogruppi di IBS secondo le caratteristiche delle feci

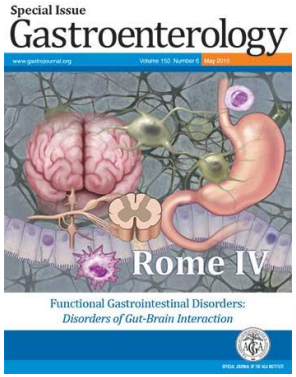


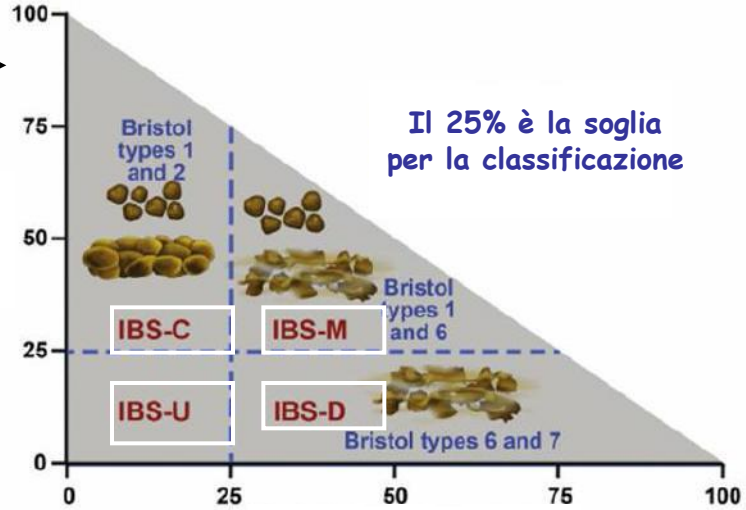
Forma delle feci scala Bristol (Lewis e Heaton, 1997, mod.)

- insorgenza o variazione dei sintomi dopo i 50 anni ?
- dimagrimento
- sangue nelle feci
- anemia
- febbre
- anemia
- tumefazioni addominali
- risveglio notturno causato dai disturbi

Tabella III : Sintomi e Segni di Allarme da considerare nei pazienti con sospetta IBS

Dure/Grumose %





Il 25% è la soglia per la classificazione

Diarrea sciolta/acquosa %

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Mauro Mario Amato
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SINDROME DELL'INTESTINO IRRITABILE (IBS)

Laboratorio

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Indagini di laboratorio:

- VES, PCR e ß2-Microglobulina
- Calprotectina/Lattoferrina fecale
- Sideremia e Ferritina
- FOB ed Esame urine
- Anti-Transglutaminasi tissutale IgA e IgA totali

Indagini di seconda istanza:

- **Studio Ormonale** (steroidi sessuali e corticosteroidi, tiroidei, gastrina, somatostatina, motilina, serotonina)
- **OCT** (velocità di transito oro-cecale)
- **Zonulina**

- **Anti-CdtB** (Cytolethal Distending toxin B)
- **Anti-Vinculina**

Test di 2^ generazione che differenziano IBS-D dalle MICI

CDT (proteina batterica) induce rotture del doppio filamento del DNA con morte cellulare o mutagenesi

Vinculina proteina per l'ancoraggio filamenti actina/citoscheletro alla membrana cellulare.

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Format: Abstract

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Dig Dis Sci. 2019 May 31. doi: 10.1007/s10620-019-05684-6. [Epub ahead of print]

Second-Generation Biomarker Testing for Irritable Bowel Syndrome Using Plasma Anti-CdtB and Anti-Vinculin Levels.

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Anti-CdtB/Anti-Vinculina elevati in IBS rispetto ai IBD

Abstract

BACKGROUND: ELISA testing for anti-CdtB and anti-vinculin can discriminate patients with irritable bowel syndrome with diarrhea (IBS-D) from those with inflammatory bowel disease (IBD). However, recent findings suggest the antigens can suffer from epitope instability.

AIM: This study aimed to assess effects of incorporating epitope stabilization on test characteristics for distinguishing IBS-D from IBD subjects.

METHODS: Plasma samples from IBS-D subjects from a large-scale clinical trial and subjects with endoscopically active IBD without concurrent immunomodulator therapy were used. After epitope stabilization, CdtB and vinculin were used in ELISA testing. Optical density readings were compared between IBS-D and IBD subjects.

RESULTS: Samples from 100 IBS-D and 31 IBD (22 UC and 9 CD) subjects were tested. IBS-D subjects had higher anti-CdtB titers ($P = 0.0001$) and higher anti-vinculin titers ($P = 0.004$) than IBD subjects. The specificities of anti-CdtB and anti-vinculin to differentiate IBS-D from IBD were 93.5% and 90.9%, respectively, with sensitivities of 43.0% and 52.2%, respectively. The positive likelihood ratios of identifying IBS-D with anti-CdtB and anti-vinculin were 6.7 and 5.7, respectively. Assuming a pretest probability of 57% for diagnosis of IBS-D in patients with abdominal pain and change in bowel habits, testing positive for both antibodies resulted in a posttest probability of > 98%.

CONCLUSIONS: Performing epitope stabilization for CdtB and vinculin enhances the test characteristics of ELISAs for anti-CdtB and anti-vinculin in discriminating IBS-D from IBD. Measurement of anti-CdtB and anti-vinculin with this second-generation methodology may further advance our understanding of the role of immunity in functional bowel diseases.

https://www.ncbi.nlm.nih.gov/pubmed/31152332

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Journal List > United European Gastroenterol J > v.7(5); 2019 Jun > PMC6545708

UNITED EUROPEAN GASTROENTEROLOGY ueg journal SAGE

United European Gastroenterol J. 2019 Jun; 7(5): 709–715.
Published online 2019 Jan 19. doi: 10.1177/2050640619826419

PMCID: PMC6545708
PMID: 31210949

Serum zonulin is elevated in IBS and correlates with stool frequency in IBS-D

Prashant Singh,[1] Jocelyn Silvester,[1,2] Xinhua Chen,[1] Hua Xu,[1] Veer Sawhney,[1] Vikram Rangan,[1] Johanna Iturrino,[1] Judy Nee,[1] Donald R. Duerksen,[3] and Anthony Lembo[1]

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Abstract

Go to:

Correlazione diretta Zonulina/IBS-D

Background

Studies have shown increased intestinal permeability in irritable bowel syndrome. Validating serum biomarkers for altered intestinal permeability in irritable bowel syndrome will facilitate research and pathophysiology-based therapy.

Objective

To measure serum zonulin and intestinal fatty acid binding protein levels in diarrhea-predominant irritable bowel syndrome and constipation-predominant irritable bowel syndrome and compare with healthy controls and celiac disease.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6545708/

United European Gastroenterol J

Zonulina sierica ↑ in IBS e Celiachia

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In presenza di sintomi principali: Dolore addominale – Diarrea – Febbre – Perdita di peso

Esclusione Celiachia

- Anti-tTG
- IgA totali
- Anti-DGP
- Anti-EMA
- Indagine genetica HLA DQ2-DQ8

Dosaggio Calprotectina fecale

- < 50 µg/g → **IBS Disordine funzionale** → Ulteriori indagini per IBS
- 50-200 µg/g → **Bassa attività infiammatoria MICI in remissione** → Ulteriori indagini (imaging, biopsia)
- > 200 µg/g → **Alta attività infiammatoria MICI stadio attivo** → Differenziazione CD/UC (sierologia per ASCA/ANCA)

Esclusione Gastroenteriti infettive

- Sangue occulto e leucociti fecali
- Tossina A/B Clostridium difficile
- Viro-immunologia: HBV, HCV, HIV, EBV, CMV
- Coprocoltura e parassitologico feci

Tratto da ORGENTEC Diagnostika

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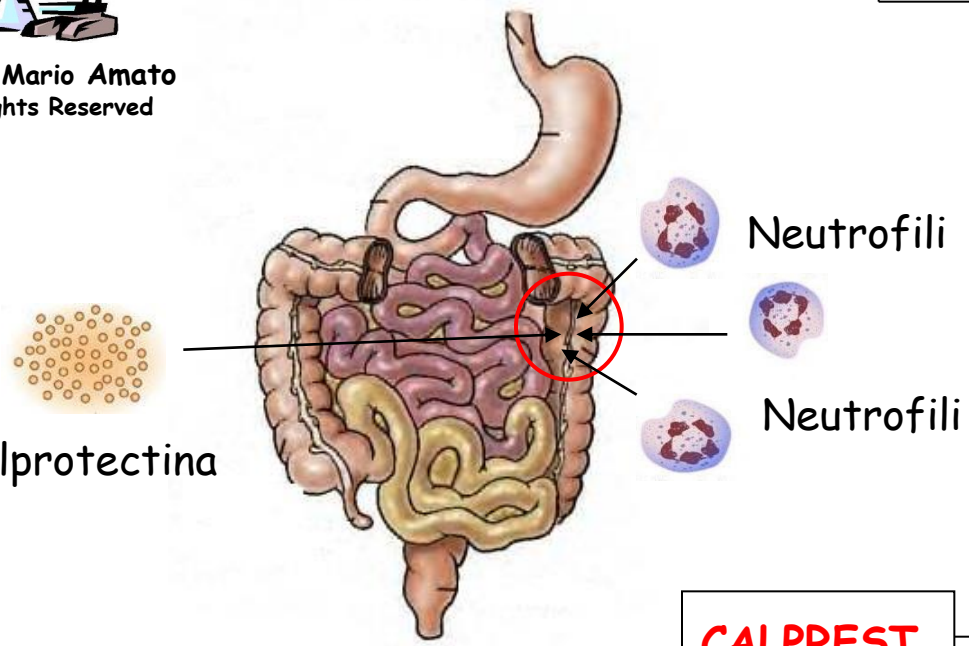
CALPROTECTINA FECALE



- **Proteina antimicrobica** (legante il calcio) essenzialmente presente nei neutrofili.
  La sua presenza nelle feci è utilizzata come **indice di infiltrazione di neutrofili** nel lume intestinale.

Calprotectina fecale

CALPREST

- Test per la determinazione della calprotectina fecale (**marker di flogosi intestinale**).
  Verifica, in modo non invasivo la presenza di uno **stato infiammatorio intestinale**.
- La calprotectina fecale **aumenta** in oltre il **95% dei pazienti con MICI**.

- Il Calprest può **differenziare** (in modo affidabile) i soggetti con **MICI** da quelli con **IBS**
- Il **Calprest negativo esclude** (con quasi certezza) **una infiammazione della mucosa intestinale**
- Usato anche in casi pediatrici

Dosaggio immunochimico

Valori riferimento
border-line **35-50 ug/g feci**

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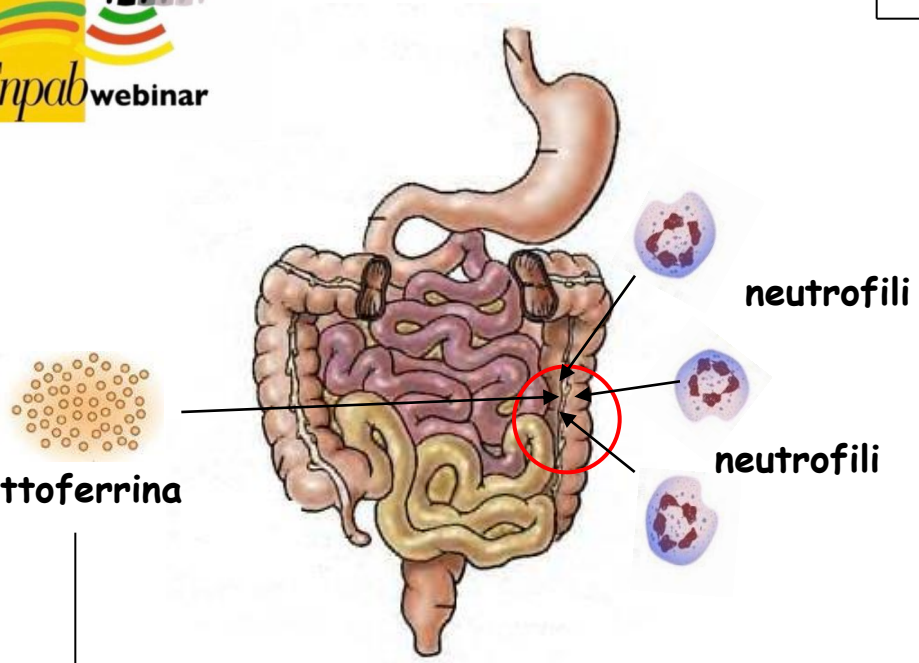
LATTOFERRINA FECALE



- Detta anche Lattotransferrina è proteina legante il ferro **presente come "scorta" nei granuli dei neutrofili**.
- La sua presenza nelle feci è utilizzata come **indice di infiltrazione di neutrofili** nel lume intestinale (marker di flogosi intestnale)
- Come la calprotectina verifica, in modo non invasivo la presenza di uno **stato infiammatorio intestinale**.
- La **lattoferrina** e **calprotectina** fecale **aumentano** nel **95-98% dei pazienti con MICI**
  Dosaggio utile al **monitoraggio dello status di malattia**

Lattoferrina fecale

Dosaggio immunochimico

Assente in condizioni normali

- Il **Calprest e Lattoferrina negativi escludono** (con quasi totale certezza) **una infiammazione della mucosa intestinale**
- Usato anche in casi pediatrici

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PMID: 30026921

The gut microbiome and irritable bowel syndrome

Stacy Menees, Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing[1,2] and William Chey, Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing[a,1]

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Competing interests: WDC is a consultant for Ironwood Pharmaceuticals and is a patent holder and principal at My Total Health. SM declares that she has no competing interests.

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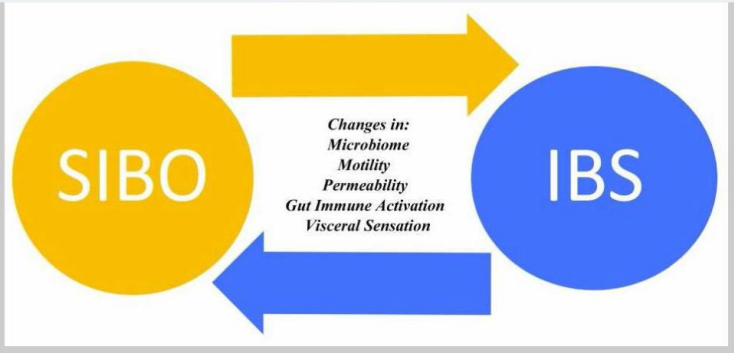
Abstract

Go to:

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders encountered in clinical practice. It is a heterogeneous disorder with a multifactorial pathogenesis. Recent studies have demonstrated that an imbalance in gut bacterial communities, or "dysbiosis", may be a contributor to the pathophysiology of IBS. There is evidence to suggest that gut dysbiosis may lead to activation of the gut immune system with downstream effects on a variety of other factors of potential relevance to the pathophysiology of IBS. This review will highlight the data addressing the emerging role of the gut microbiome in the pathogenesis of IBS and review the evidence for current and future microbiome based treatments

Ruolo microbioma patogenesi IBS



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6039952/

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Disbiosi → SIBO (Small Intestinal Bacterial Overgrowth)
Sovracrescita Batterica del Tenue

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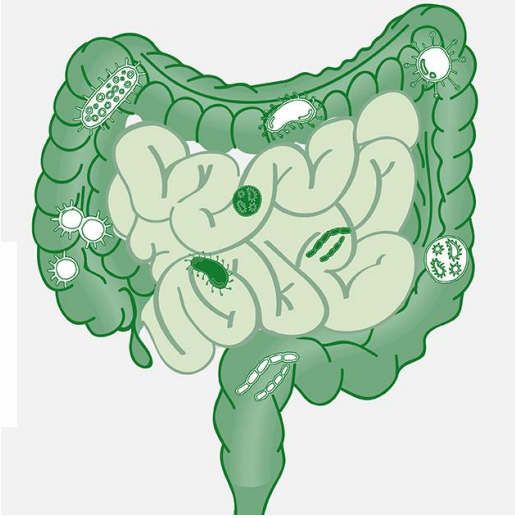
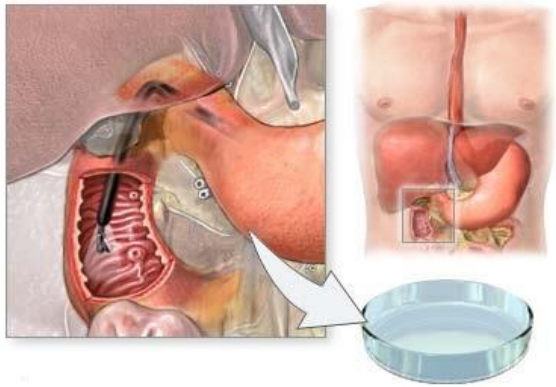
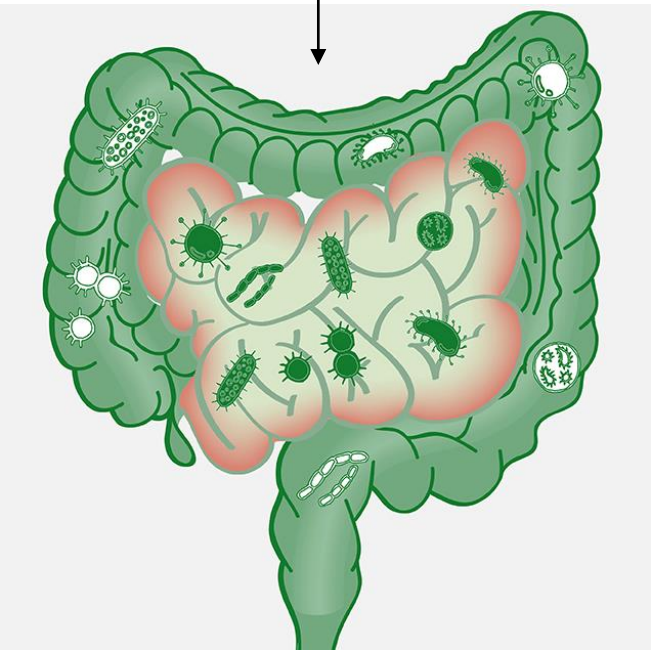


Normalmente il tenue possiede una **minima concentrazione di flora microbica non in grado di fermentare i carboidrati**.

La **SIBO** è invece caratterizzata dalla **presenza nel tenue di batteri carboidrati-fermentanti** causa di disturbi intestinali.





Test Gold-Standard

Aspirato/coltura dell'intestino tenue

Significatività clinica con crescita di **103-105 ufc/ml**

Test invasivo

SIBO

Sovracrescita Batterica del Tenue - Sintomatologia

- Perdita di peso
- Malnutrizione
- Vomito
- Diarrea
- Nausea
- Gonfiore
- Depressione
- Asma
- Eczema
- Acne
- Rash
- Fatica
- Rosacea
- Dolori articolari

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SIBO (Small Intestinal Bacterial Overgrowth)
H2-GLUCOSIO BREATH TEST

AB H2-GLUCOSIO breath test

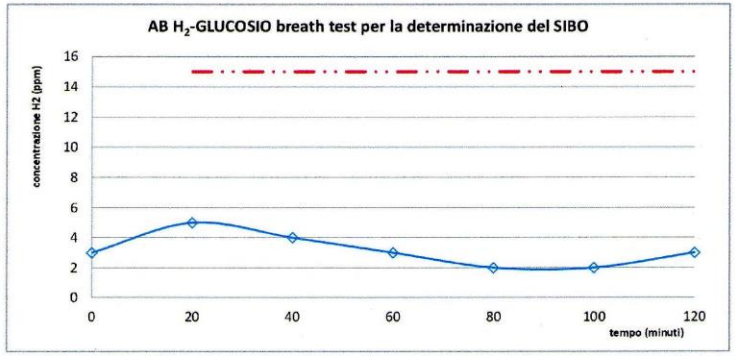
Test per la determinazione della sovracrescita batterica nell'intestino tenue
(SIBO: small intestine bacterial overgrowth)

NOME	[redacted]
DATA DI NASCITA	[redacted]

data dell'esame	19\11\2018	
dose substrato	50	(grammi)
cut-off (DOB)	12	(ppm H_2)

S/N strumento	2014 - 3304
versione SW	2.05

n°	Tempo (minuti)	conc. H_2 (ppm)	DOB
1	0	3	
2	20	5	2
3	40	4	1
4	60	3	0
5	80	2	-1
6	100	2	-1
7	120	3	0



CRITERIO D'INTERPRETAZIONE

una concentrazione di H2 nel basale (ppm T0) >10 ppm indica che il paziente probabilmente non è stato a digiuno nelle ore precedenti al test.
la concentrazione d'idrogeno nell'espirato basale (T0) è 3 ppm

un DOB (delta over base) > 12 ppm H2 rispetto a T0, indica un paziente positivo al test
il picco della concentrazione d'idrogeno nell' intervallo da 20 a 120 minuti è 5 ppm a 20 minuti
l'incremento DOB(max) è 2 ppm H2

RISULTATO: negativo

IL BIOLOGO RESPONSABILE

Indagine di laboratorio per la **determinazione della SIBO**

Il **protocollo standard** prevede:
- Informativa al circa l'esecuzione del test
- Misurazione concentrazione di H2 nell'espirato (**T0**)
- Somministrazione di **50 g di Glucosio** solubilizzati in 200 ml di acqua dopo un digiuno di almeno 10 ore
- Misurazione della concentrazione di H2 nell'espirato ai tempi **T20, T40, T60, T80, T100, T120**
- **Elaborazione dei dati**

Condizioni Normali

Il glucosio viene completamente assorbito a livello del digiuno e quindi **non si rileva un aumento della concentrazione di H2**

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NORME DI PREPARAZIONE

H_2-Breath test (Lattosio, Lattulosio, Glucosio, Fruttosio)

Informativa al paziente

5-7 giorni precedente il test

Alimenti da evitare:
- Fermenti lattici e yogurt
- Latte e derivati (latte animale)
- Preparati contenenti latte
- Salumi e affettati contenenti lattosio

Alimenti consentiti:
- Prodotti a base di soia
- Latte di mandorla
- Riso e suoi preparati

DIETA DEL GIORNO PRIMA DEL TEST

Colazione: libera (evitando gli alimenti di cui sopra)
Pranzo: piatto di riso bollito con poco olio (entro le 14.30)
Cena: carne o pesce e insalata con poco olio e sale (no limone)

Astenersi da pasti intermedi

Farmaci da evitare:
- **Antibiotici**, **lassativi**, **antiacidi** e **inibitori di pompa** (almeno 15-20 gg)
- **Farmaci non essenziali** (da 12h prima del test)

Il paziente non deve avere in corso diarrea significativa

Dalle ore 21.00 del giorno precedente digiuno completo senza fumare (può bere liberamente acqua non gassata).
Digiuno di circa 10-12 ore

La mattina dell'esame:
- Lavaggio accurato dei denti
- Pulizia cavo orale (con colluttorio se necessario)
- Non svolgere attività fisica e non fumare

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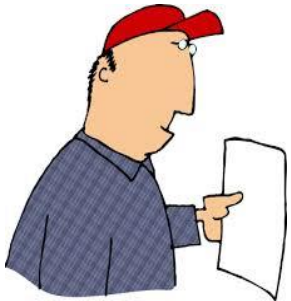

SIBO (Small Intestinal Bacterial Overgrowth)

H2-GLUCOSIO BREATH TEST

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AB H2-GLUCOSIO breath test

Test per la determinazione della sovracrescita batterica nell'intestino tenue
(SIBO: small intestine bacterial overgrowth)

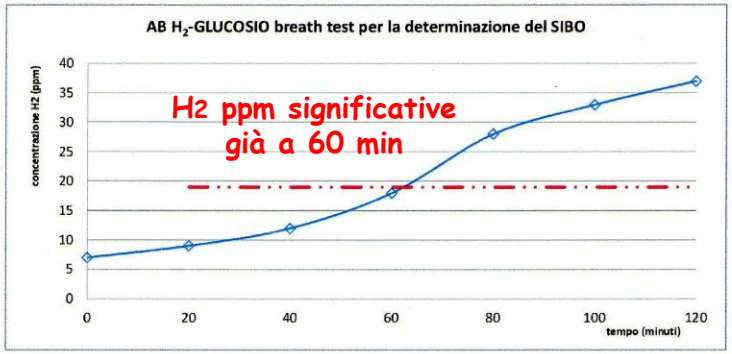
NOME	[redacted]
DATA DI NASCITA	[redacted]

data dell'esame	28/05/2019	
dose substrato	50	(grammi)
cut-off (DOB)	12	(ppm H_2)

S/N strumento	2014 - 3304
versione SW	2.05

n°	Tempo (minuti)	conc. H_2 (ppm)	DOB
1	0	7	
2	20	9	2
3	40	12	5
4	60	18	11
5	80	28	21
6	100	33	26
7	120	37	30

DOB (Delta Over Base) > 12 ppm rispetto al T0



CRITERIO D'INTERPRETAZIONE

una concentrazione di H2 nel basale (ppm T0) >10 ppm indica che il paziente probabilmente non è stato a digiuno nelle ore precedenti al test.
la concentrazione d'idrogeno nell'espirato basale (T0) è 7 ppm
un DOB (delta over base) > 12 ppm H2 rispetto a T0, indica un paziente positivo al test
il picco della concentrazione d'idrogeno nell' intervallo da 20 a 120 minuti è 37 ppm a 120 minuti
l'incremento DOB(max) è 30 ppm H2

RISULTATO: POSITIVO

IL BIOLOGO RESPONSABILE

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e-mail lab.amato@virgilio.it

AB H2-GLUCOSIO breath test

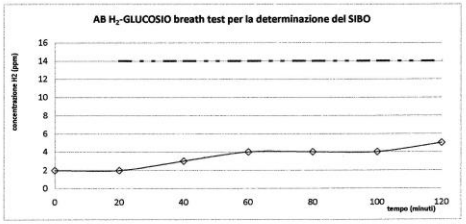
Test per la determinazione della sovracrescita batterica nell'intestino tenue
(SIBO: small intestine bacterial overgrowth)

NOME	[redacted]
DATA DI NASCITA	[redacted]

data dell'esame	06/06/2016	
dose substrato	50	(grammi)
cut-off (DOB)	12	(ppm H_2)

S/N strumento	2014 - 3304
versione SW	2.05

n°	Tempo (minuti)	conc. H_2 (ppm)	DOB
1	0	2	
2	20	2	0
3	40	3	1
4	60	4	2
5	80	4	2
6	100	4	2
7	120	5	3



CRITERIO D'INTERPRETAZIONE

una concentrazione di H2 nel basale (ppm T0) >10 ppm indica che il paziente probabilmente non è stato a digiuno nelle ore precedenti al test.
la concentrazione d'idrogeno nell'espirato basale (T0) è 2 ppm
un DOB (delta over base) > 12 ppm H2 rispetto a T0, indica un paziente positivo al test
il picco della concentrazione d'idrogeno nell' intervallo da 20 a 120 minuti è 5 ppm a 120 minuti
l'incremento DOB(max) è 3 ppm H2

RISULTATO: negativo

IL BIOLOGO RESPONSABILE

Condizioni Normali

Condizione di SIBO

Il **glucosio fermentato nel tenue** (digiuno) e questo comporta un **aumento della concentrazione di H2** nell'espirato con valori di ppm già significativi a 60 min

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SIBO

H_2-GLUCOSIO Breath test vs H_2-LATTULOSIO Breath test

Accuratezza diagnostica stimata 72%

Meno probabilità di falsi positivi
(glucosio ben assorbito e poco probabile che raggiunga il colon)

SIBO ileale spesso non evidenziabile
(in genere glucosio tutto assorbito prima)

Non idoneo per soggetti diabetici

Non idoneo per soggetti non-H_2 producer
(associazione con la **misurazione del CH_4**)

Accuratezza diagnostica stimata 54%

Più probabilità di falsi positivi
(lattulosio non assorbito e può raggiungere il colon)

SIBO ileale spesso evidenziabile
(lattulosio non assorbito e raggiunge l'ileo)

Idoneo per soggetti diabetici

Non idoneo per soggetti con tempo di transito intestinale aumentato

Risultati associati all'età e sesso

Non idoneo per non-H_2 producer
(misurazione **CH_4**)

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Various available BTs which are in use in clinical practice with their reported sensitivities and specificities are listed in (Table 3).

SENSIBILITÀ= probabilità che un **malato** risulti **positivo**

SPECIFICITÀ= probabilità che un **sano** risulti **negativo**

Table 3

Representative diagnostic accuracy in terms of sensitivity and specificity of various breath tests available for clinical use

Test	Indication	Sensitivity and specificity
Glucose hydrogen breath test	SIBO	62% and 83%[7]
Lactulose hydrogen breath test	SIBO	31% and 86%[5]
13C-glycocholate breath test	SIBO	76% and 33%[69]
13C-xylose breath test	SIBO	89% and 30%[69]
Fructose hydrogen breath test	Carbohydrate malabsorption	98% and 86%[65]
Lactose hydrogen breath test	Carbohydrate malabsorption	80% and 100%[66]
13C-lactose breath test	Carbohydrate malabsorption	84% and 96%[70]
13C-urea breath test	*H. pylori* infection	96% and 93%[39]
13C-aminopyrine breath test	Evaluation of liver function	85.7% and 67.5%[58]
13C-methacetin breath test	Evaluation of liver function	92.6% and 94.1%[67]
13C-phenacetin breath test	Evaluation of liver function	98% and 60%[68]
13C-mixed triglycerides breath test	Evaluation of exocrine pancreatic insufficiency	89% and 81%[56]
13C-octanoic acid breath test	Assessment of gastric emptying	67% and 80%[71]

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Update on diagnostic value of breath test in gastrointestinal and liver diseases
World J Gastrointest Pathophysiol. 2016 Aug 15; 7(3): 256-265

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Lactulose Hydrogen Breath Test Result Is Associated with Age and Gender

Carolyn Newberry,[1] Ann Tierney,[2] and Octavia Pickett-Blakely[1,*]

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*Octavia Pickett-Blakely: octavia.pickett-blakely@uphs.upenn.edu

Academic Editor: Luca Elli

SIBO Lattulosio-BT
donne: aumento probabilità positivi con l'età
uomini: diminuzione positivi con l'età

Abstract

Small intestinal bacterial overgrowth (SIBO) is associated with chronic gastrointestinal diseases and structural/functional abnormalities of the gastrointestinal tract. SIBO's association with clinical characteristics is unclear. This study investigates the association between clinical factors and SIBO according to lactulose hydrogen breath test (LHBT) result. *Methods*. A cross-sectional study in a university-based gastroenterology practice was performed. Data was abstracted from the medical records of subjects undergoing LHBT from 6/1/2009 to 6/1/2013. Logistic regression analysis was performed to determine the association between predictor variables: age, sex, body mass index (BMI), and positive LHBT, the outcome of interest. *Results*. LHBT was performed in 791 subjects. Fifty-four percent had a positive LHBT. There was no statistically significant difference between the LHBT results according to age or BMI. In females, the likelihood of a positive LHBT increased with age (OR 1.02; 95% CI: 1.01–1.03). In males, the likelihood of a positive LHBT result decreased with age (OR 0.98; 95% CI: 0.97–1.00). *Conclusion*. There was an association between age, with respect to sex, and a positive LHBT. With increased age in females, the odds of a positive LHBT increased, while, in men, the odds of a positive LHBT decreased with age.

Biomed Res Int

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4814632/

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REVIEW ARTICLE
Front. Pediatr., 04 September 2019 | https://doi.org/10.3389/fped.2019.00363

Small Intestinal Bacterial Overgrowth in Children: A State-Of-The-Art Review

David Avelar Rodriguez[1*], Paul MacDaragh Ryan[2], Erick Manuel Toro Monjaraz[1], Jaime Alfonso Ramirez Mayans[1] and Eamonn Martin Quigley[3]

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Stato dell'arte sulla SIBO pediatrica

Small intestinal bacterial overgrowth (SIBO) is a heterogenous and poorly understood entity characterised by an excessive growth of select microorganisms within the small intestine. This excessive bacterial biomass, in turn, disrupts host physiology in a myriad of ways, leading to gastrointestinal and non-gastrointestinal symptoms and complications. SIBO is a common cause of non-specific gastrointestinal symptoms in children, such as chronic abdominal pain, abdominal distention, diarrhoea, and flatulence, amongst others. In addition, it has recently been implicated in the pathophysiology of stunting, a disease that affects millions of children worldwide. Risk factors such as acid-suppressive therapies, alterations in gastrointestinal motility and anatomy, as well as impoverished conditions, have been shown to predispose children to SIBO. SIBO can be diagnosed via culture-dependant or culture-independent approaches. SIBO's epidemiology is limited due to the lack of uniformity and consensus of its diagnostic criteria, as well as the paucity of literature available. Antibiotics remain the first-line treatment option for SIBO, although emerging modalities such as probiotics and diet manipulation could also have a role. Herein, we present a state-of-the-art-review which aims to comprehensively outline the most current information on SIBO in children, with particular emphasis on the gut microbiota.

Mauro Amato

https://www.frontiersin.org/articles/10.3389/fped.2019.00363/full

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Meta-analysis

Enpab webinar

Breath Tests for the Non-invasive Diagnosis of Small Intestinal Bacterial Overgrowth: A Systematic Review With Meta-analysis

SIBO Revisione sistematica con meta-analisi

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Background/Aims
Small intestinal bacterial overgrowth (SIBO) diagnosis is usually based on non-invasive breath tests (BTs), namely lactulose BT (LBT) and glucose BT (GBT). However, divergent opinions and problems of parameter standardization are still controversial aspects. We aim to perform a meta-analysis to analyze diagnostic performance of LBT/GBT for SIBO diagnosis.

Methods
We searched in main literature databases articles in which SIBO diagnosis was achieved by LBT/GBT in comparison to jejunal aspirate culture (reference gold standard). We calculated pooled sensitivity, specificity, positive, and negative likelihood ratios and diagnostic odd ratios. Summary receiver operating characteristic curves were drawn and pooled areas under the curve were calculated.

Results
We selected 14 studies. Pooled sensitivity of LBT and GBT was 42.0% and 54.5%, respectively. Pooled specificity of LBT and GBT was 70.6% and 83.2%, respectively. When delta over baseline cut-off > 20 H_2 parts per million (ppm) was used, GBT sensitivity and specificity were 47.3% and 80.9%; when the cutoff was other than and lower than > 20 ppm, sensitivity and specificity were 61.7% and 86.0%. In patients with abdominal surgery history, pooled GBT sensitivity and specificity gave the impression of having a better performance (81.7% and 78.8%) compared to subjects without any SIBO predisposing condition (sensitivity = 40.6% and specificity = 84.0%).

Conclusions
GBT seems to work better than LBT. A cut-off of delta H2 expired other than and lower than > 20 ppm shows a slightly better result than > 20 ppm. BTs demonstrate the best effectiveness in patients with surgical reconstructions of gastrointestinal tract.
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Mauro Amato

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6955189/

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REVIEW ARTICLE

Small Intestinal Bacterial Overgrowth: Clinical Features and Therapeutic Management

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OPEN

Metrics

Abstract

SIBO Gestione Clinica e Terapeutica

Small intestinal bacterial overgrowth (SIBO) is a common, yet underrecognized, problem. Its prevalence is unknown because SIBO requires diagnostic testing. Although abdominal bloating, gas, distension, and diarrhea are common symptoms, they do not predict positive diagnosis. Predisposing factors include proton-pump inhibitors, opioids, gastric bypass, colectomy, and dysmotility. Small bowel aspirate/culture with growth of 10^3–10^5 cfu/mL is generally accepted as the "best diagnostic method," but it is invasive. Glucose or lactulose breath testing is noninvasive but an indirect method that requires further standardization and validation for SIBO. Treatment, usually with antibiotics, aims to provide symptom relief through eradication of bacteria in the small intestine. Limited numbers of controlled studies have shown systemic antibiotics (norfloxacin and metronidazole) to be efficacious. However, 15 studies have shown rifaximin, a nonsystemic antibiotic, to be effective against SIBO and well tolerated. Through improved awareness and scientific rigor, the SIBO landscape is poised for transformation.

Mauro Amato

https://journals.lww.com/ctg/fulltext/2019/10000/small_intestinal_bacterial_overgrowth__clinical.2.aspx

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SIBO

AB H2-LATTOSIO breath test

Test per la determinazione di ipolactasia e intolleranza al lattosio

NOME	[redacted] Luciana
DATA DI NASCITA	[redacted]

data dell'esame	21/09/18	
dose substrato	25	(grammi)
cut-off (DOB)	20	(ppm H_2)

S/N strumento	2014 - 3304
versione SW	2.05

n°	Tempo (minuti)	conc. H_2 (ppm)	DOB
1	0	9	
2	30	16	7
3	60	80	71
4	90	68	59
5	120	60	51
6	150	70	61
7	180	50	41
8	210	33	24
9	240	48	39

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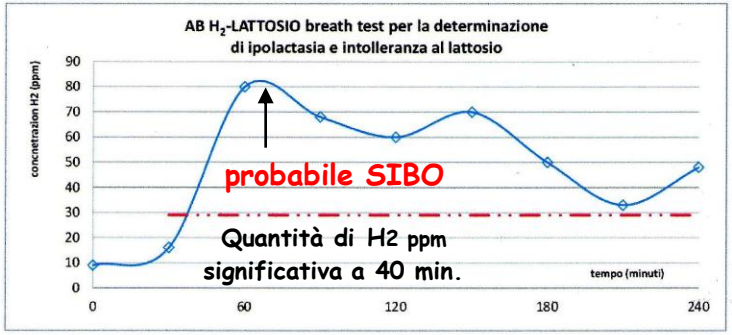

CRITERIO D'INTERPRETAZIONE

una concentrazione di H2 nel basale (ppm T0) >10 ppm indica che il paziente probabilmente non è stato a digiuno nelle ore precedenti al test.
la concentrazione d'idrogeno nell'espirato basale (T0) è 9 ppm

un DOB (delta over base) > 20 ppm H2 rispetto a T0, indica un paziente positivo al test
il picco della concentrazione d'idrogeno nell' intervallo da 20 a 240 minuti è 80 ppm a 60 minuti
l'incremento DOB(max) è 71 ppm H2

RISULTATO: POSITIVO

IL BIOLOGO RESPONSABILE

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AB H2-GLUCOSIO breath test

Test per la determinazione della sovracrescita batterica nell'intestino tenue
(SIBO: small intestine bacterial overgrowth)

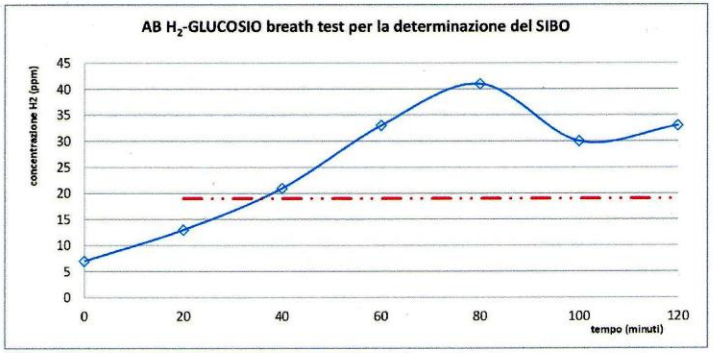
NOME	[redacted] Luciana
DATA DI NASCITA	[redacted]

data dell'esame	28/09/2018	
dose substrato	50	(grammi)
cut-off (DOB)	12	(ppm H_2)

S/N strumento	2014 - 3304
versione SW	2.05

n°	Tempo (minuti)	conc. H_2 (ppm)	DOB
1	0	7	
2	20	13	6
3	40	21	14
4	60	33	26
5	80	41	34
6	100	30	23
7	120	33	26

Enpab webinar



CRITERIO D'INTERPRETAZIONE

una concentrazione di H2 nel basale (ppm T0) >10 ppm indica che il paziente probabilmente non è stato a digiuno nelle ore precedenti al test.
la concentrazione d'idrogeno nell'espirato basale (T0) è 7 ppm

un DOB (delta over base) > 12 ppm H2 rispetto a T0, indica un paziente positivo al test
il picco della concentrazione d'idrogeno nell' intervallo da 20 a 120 minuti è 41 ppm a 80 minuti
l'incremento DOB(max) è 34 ppm H2

RISULTATO: POSITIVO

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DIABETICO con IBS

AB H2-LATTULOSIO breath test

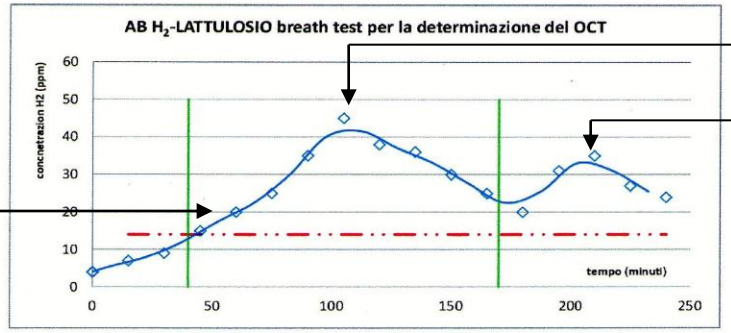
Test per la determinazione del tempo di transito oro-cecale (OCT)

NOME	[redacted] Nicola
DATA DI NASCITA	[redacted]

data del esame	16/07/19	
dose substrato	10	(grammi)
cut-off (DOB)	10	(ppm H_2)
rif. intervallo OCT	da 40 a 170 minuti	

S/N strumento	2014 - 3304
versione SW	2.05

n°	Tempo (minuti)	conc. H_2 (ppm)	n°	Tempo (minuti)	conc. H_2 (ppm)
1	0	4	10	135	36
2	15	7	11	150	30
3	30	9	12	165	25
4	45	15	13	180	20
5	60	20	14	195	31
6	75	25	15	210	35
7	90	35	16	225	27
8	105	45	17	240	24
9	120	38			



SIBO
(picco a 113 min)

OCT= 210 min

Quantità di H2 ppm significativa a 75 min.

CRITERIO D'INTERPRETAZIONE

una concentrazione di H_2 nel basale (ppm T_0) >10 ppm indica che il paziente probabilmente non è stato a digiuno nelle ore precedenti al test

la concentrazione d'idrogeno nell'espirato basale (T0) è 4 ppm

un DOB (delta over base) > 10 ppm H2 rispetto a T0 nell' intervallo da 40 a 170 minuti indica un OCT normale. Nel caso si verifichino due picchi, il primo è attribuibile alla presenza di sovracrescita batterica (SIBO) ed il secondo all'OCT.

ci sono due picchi, il primo a 113 minuti è un sospetto SIBO, e il secondo è a 173 minuti con una concentrazione di 33 ppm H2. L'OCT è 210 minuti.

RISULTATO: **OCT rallentato**

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SIBO

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AB H2-LATTULOSIO breath test

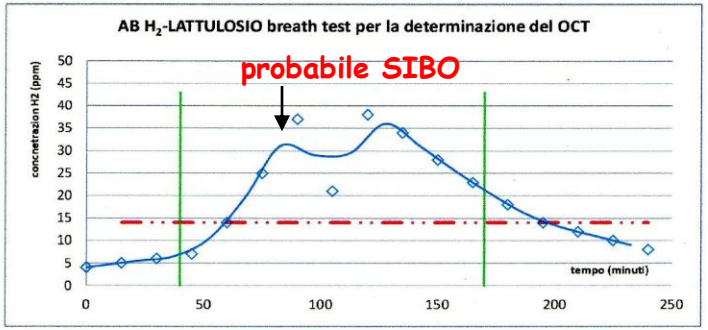
Test per la determinazione del tempo di transito oro-cecale (OCT)

NOME	[redacted] Ruggiero
DATA DI NASCITA	[redacted]

data del esame	13/04/19	
dose substrato	10	(grammi)
cut-off (DOB)	10	(ppm H_2)
rif. intervallo OCT	da 40 a 170 minuti	

S/N strumento	2014 - 3304
versione SW	2.05

n°	Tempo (minuti)	conc. H_2 (ppm)	n°	Tempo (minuti)	conc. H_2 (ppm)
1	0	4	10	135	34
2	15	5	11	150	28
3	30	6	12	165	23
4	45	7	13	180	18
5	60	14	14	195	14
6	75	25	15	210	12
7	90	37	16	225	10
8	105	21	17	240	8
9	120	38			



CRITERIO D'INTERPRETAZIONE

una concentrazione di H_2 nel basale (ppm T_0) >10 ppm indica che il paziente probabilmente non è stato a digiuno nelle ore precedenti al test

la concentrazione d'idrogeno nell'espirato basale (T0) è 4 ppm

un DOB (delta over base) > 10 ppm H2 rispetto a T0 nell' intervallo da 40 a 170 minuti indica un OCT normale. Nel caso si verifichino due picchi, il primo è attribuibile alla presenza di sovracrescita batterica (SIBO) ed il secondo all'OCT.

ci sono due picchi, il primo a 83 minuti è un sospetto SIBO, e il secondo è a 128 minuti con una concentrazione di 36 ppm H2. L'OCT è 135 minuti.

RISULTATO: **OCT NORMALE**

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AB H2-GLUCOSIO breath test

Test per la determinazione della sovracrescita batterica nell'intestino tenue
(SIBO: small intestine bacterial overgrowth)

NOME	[redacted] O Ruggero
DATA DI NASCITA	[redacted]

data dell'esame	19/04/2019	
dose substrato	50	(grammi)
cut-off (DOB)	12	(ppm H_2)

S/N strumento	2014 - 3304
versione SW	2.05

n°	Tempo (minuti)	conc. H_2 (ppm)	DOB
1	0	7	
2	20	10	3
3	40	15	8
4	60	23	16
5	80	35	28
6	100	30	23
7	120	26	19

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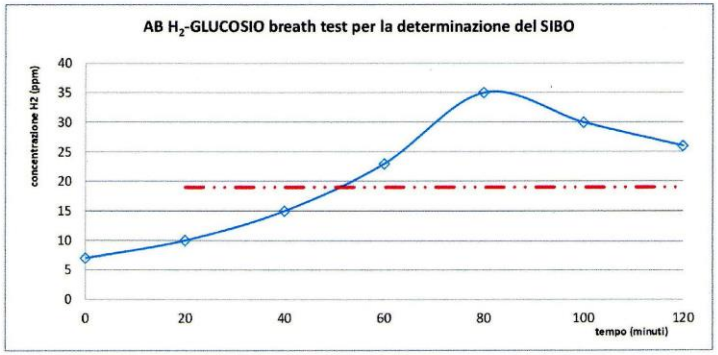


CRITERIO D'INTERPRETAZIONE

una concentrazione di H2 nel basale (ppm T0) >10 ppm indica che il paziente probabilmente non è stato a digiuno nelle ore precedenti al test.

la concentrazione d'idrogeno nell'espirato basale (T0) è 7 ppm

un DOB (delta over base) > 12 ppm H2 rispetto a T0, indica un paziente positivo al test

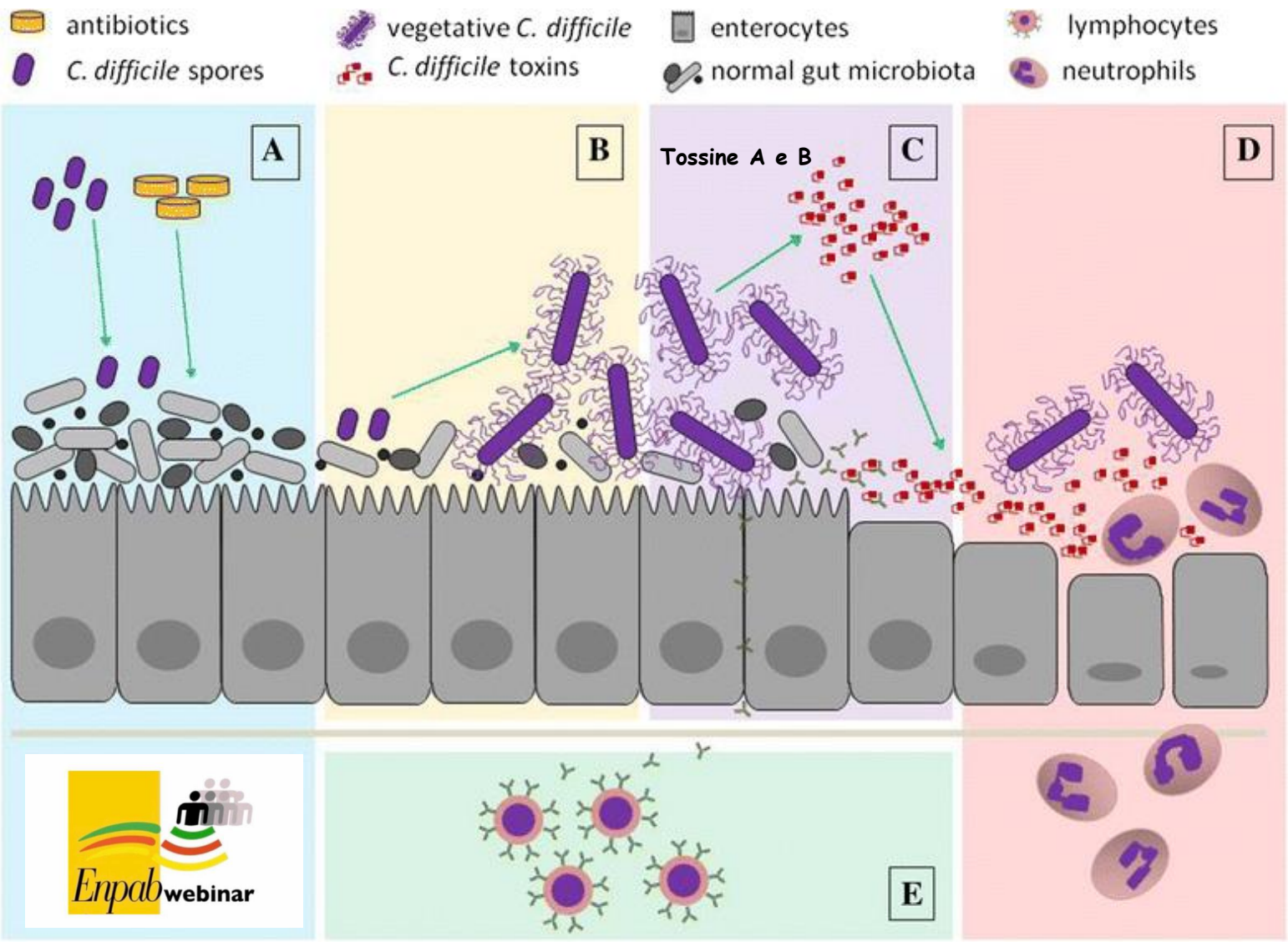
il picco della concentrazione d'idrogeno nell' intervallo da 20 a 120 minuti è 35 ppm a 80 minuti

l'incremento DOB(max) è 28 ppm H2

RISULTATO: **POSITIVO**

IL BIOLOGO RESPONSABILE

DISBIOSI → INFEZIONE DA CLOSTRIDIUM DIFFICILE



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Infectious Diseases and Therapy March 2017, Volume 6

DISBIOSI → INFEZIONE DA CLOSTRIDIUM DIFFICILE (Diagnosi di Laboratorio)

Campione feci

Linee guida ISDA →

- Determinazione **Tossina A** (Immunochimica/Immunocromatografia)
- Determinazione **Tossina B** (Immunochimica/Immunocromatografia)
- Determinazione **C.difficile GDH** (Immunochimica/Immunocromatografia)

C. difficile utilizza durante la sua crescita grande quantità di **acido glutammico**

Citotossina principale responsabile delle lesioni della mucosa intestinale

Enterotossina causa di diarrea e lesioni della mucosa

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Spore germinative → **Crescita vegetativa C. difficile**

↑ **inibizione**

Microbiota in EUBIOSI → **sali biliari secondari**

Grazie per la vostra attenzione

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