



## Gut microbiota in autism and mood disorders

Francesca Mangiola, Gianluca Ianiro, Francesco Franceschi, Stefano Fagioli, Giovanni Gasbarrini, Antonio Gasbarrini

Francesca Mangiola, Gianluca Ianiro, Francesco Franceschi, Antonio Gasbarrini, Catholic University, School of Medicine, 00168 Rome, Italy

Francesca Mangiola, Gianluca Ianiro, Francesco Franceschi, Antonio Gasbarrini, Department of Internal Medicine, Division of Internal Medicine, Gastroenterology and Liver Disease; "A. Gemelli" University Hospital, 00168 Rome, Italy

Stefano Fagioli, Gastroenterology and Transplant Hepatology, Papa Giovanni XXIII Hospital, 24127 Bergamo, Italy

Giovanni Gasbarrini, "Ricerca in Medicina" ONLUS Foundation, 40121 Bologna, Italy

Author contributions: All authors contributed to the manuscript.

Conflict-of-interest statement: No conflict-of-interest declared.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Antonio Gasbarrini, MD, Professor, Catholic University, School of Medicine, Largo F. Vito 1, 00168 Rome, Italy. [agasbarrini@rm.unicatt.it](mailto:agasbarrini@rm.unicatt.it)  
Telephone: +39-63-156018  
Fax: +39-63-157249

Received: June 9, 2015

Peer-review started: June 11, 2015

First decision: September 11, 2015

Revised: October 9, 2015

Accepted: November 11, 2015

Article in press: November 11, 2015

Published online: January 7, 2016

### Abstract

The hypothesis of an important role of gut microbiota in the maintenance of physiological state into the gastrointestinal (GI) system is supported by several studies that have shown a qualitative and quantitative alteration of the intestinal flora in a number of gastrointestinal and extra-gastrointestinal diseases. In the last few years, the importance of gut microbiota impairment in the etiopathogenesis of pathology such as autism, dementia and mood disorder, has been raised. The evidence of the inflammatory state alteration, highlighted in disorders such as schizophrenia, major depressive disorder and bipolar disorder, strongly recalls the microbiota alteration, highly suggesting an important role of the alteration of GI system also in neuropsychiatric disorders. Up to now, available evidences display that the impairment of gut microbiota plays a key role in the development of autism and mood disorders. The application of therapeutic modulators of gut microbiota to autism and mood disorders has been experienced only in experimental settings to date, with few but promising results. A deeper assessment of the role of gut microbiota in the development of autism spectrum disorder (ASD), as well as the advancement of the therapeutic armamentarium for the modulation of gut microbiota is warranted for a better management of ASD and mood disorders.

**Key words:** Gut microbiota; Mood disorders; Autism; Depression; Gut microbiota modulation; Fecal microbiota transplantation

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Up to now, available evidences display that the impairment of gut microbiota plays a key role in the development of autism and mood disorders.

The application of therapeutic modulators of gut microbiota to autism and mood disorders has been experienced only in experimental settings to date, with few but promising results, that suggest the microbiota modulation as a therapeutic approach for autism and mood disorders.

Mangiola F, Ianiro G, Franceschi F, Fagioli S, Gasbarrini G, Gasbarrini A. Gut microbiota in autism and mood disorders. *World J Gastroenterol* 2016; 22(1): 361-368 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i1/361.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i1.361>

## INTRODUCTION

The gut microbiota, composed of thousands of different microbial species and more than 15000 kinds of bacteria for a weight equal to 1 kg, represents the first protection system of the gastrointestinal (GI) apparatus. The presence of the microbiota varies within the gastrointestinal tract, from few microorganisms in the stomach and small intestine, up to a concentration of approximately 1.012 bacteria in the colon, mostly represented by the *Firmicutes* and *Bacteroidetes phyla*<sup>[1,2]</sup>. Within the species that compose the microbiota, it's also possible to recognize the kingdom of *Archaea* and *eukaryotes*, and many viruses and *bacteriophages*<sup>[3,4]</sup>. Finally, there were several families of fungi, whose physiological role in the gastrointestinal system is still unclear.

The functions performed by the flora are manifold; in addition to the contribution to the establishment of the intestinal barrier, it promotes its maintenance, stimulating epithelial regeneration through the production of short chain fatty acids (SCFAs), leading to mucus production and exerting a trophic action on the mucous membrane<sup>[5]</sup>.

The gut microbiota is involved in the maturation of the immune system: it stimulates innate immunity in the early years of life, leading to the maturation of the GALT, and acquired immunity, through stimulation of local and systemic immune responses<sup>[6]</sup>. Known, finally, is the role in the synthesis and metabolism of certain nutrients, hormones and vitamins, and clearance of drugs and toxic.

The human body, completely sterile at birth, is immediately in contact with a large amount of microbial communities, including the fecal, vaginal and skin microbiota of the mother. Subsequently, the composition of the flora undergoes changes, influenced by age, sex, state of immune maturation and by environmental factors.

The flora acquires its stability between 6 and 36 mo of life; in that period it's already possible to distinguish between a constant endogenous flora (core microbiota) and a still provisional one, highly sensitive to external stimuli<sup>[7,8]</sup>.

In physiological conditions, the continuous stimulation of the immune system by the gut microbiota leads to a state of "low-grade physiological inflammation", which is a rapid and effective mechanism of defence against pathogens<sup>[9]</sup>. In addition, the flora exerts its protective role competitively, metabolizing those nutrients needed for pathogens survival, and producing molecules that inhibit the growth of such microbes<sup>[10]</sup>.

Sonnenburg *et al*<sup>[11]</sup> has shown that the introduction of a compound of *Bacteroides thetaiotamicron* and *Eubacterium rectale* is able to induce the production of particular mucosal glycans, which may be metabolized exclusively by these bacterial species and not by pathogens, thus preventing their proliferation.

The hypothesis of an important role of gut microbiota in the maintenance of physiological state into the GI system is supported by several studies that have shown a qualitative and quantitative alteration of the intestinal flora in a number of gastrointestinal and extra-gastrointestinal diseases.

## GUT MICROBIOTA AND PSYCHIATRIC DISORDERS: A FOCUS ON AUTISM SPECTRUM DISORDER AND MOOD DISORDERS

Recent data show the strong correlation between dysbiosis and conditions such as obesity, allergies, autoimmune disorders, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and psychiatric disorders<sup>[12-16]</sup>.

Due to these new evidences about the fundamental role of gut microbiota in the alteration of immune, neural, and endocrine pathways, the so-called "gut-brain axis" is acquiring new significance, even if the communication routes are not still defined<sup>[16-18]</sup>.

At the beginning of the past century, first hypotheses aroused about the correlation between these two systems; probably the most practice evidence can be found in a work of an army surgeon, who noted the correlation between a patient's gut function and his mood, monitoring gastric secretions through a fistula in his stomach<sup>[13]</sup>.

In the last few years, much research has been done in this direction, underlying the importance of dysbiosis in the etiopathogenesis of pathology such as autism, dementia and mood disorder. The evidence of the inflammatory state alteration, highlighted in disorders such as schizophrenia, major depressive disorder and bipolar disorder<sup>[19-23]</sup>, strongly recalls the microbiota alteration and highly suggests an important role of the alteration of GI system also in neuropsychiatric disorders.

In particular, the dysbiosis and the consequent alteration of intestinal permeability lead respectively to the production and spread into the bloodstream of a potent pro-inflammatory endotoxine, namely

lipopolysaccharide (LPS). This small molecule has an important influence in the modulation of the central nervous system (CNS), increasing the activity of areas deputed to the emotionalism control such as amygdala<sup>[24]</sup>. It also lead to production of inflammatory cytokines that alter the physiological brain activity, modulating the neuropeptides synthesis<sup>[25]</sup>.

Rhee *et al.*<sup>[26]</sup> highlighted the importance of bidirectional connections between gut and brain that occurs in both healthy and diseased states focusing attention on enterochromaffin cells. The signals generated by the stimulation of these pathways due to intraluminal gut stimuli, running on nervous system, strongly modulate the brain activity, including pain perception, immune-response modulation, emotional control and many other homeostatic functions.

However, this influence is not unidirectional, but is a continuous communication: the CNS is able to change the composition of microbiota and to alter the equilibrium in the gut permeability, modulating motility and secretion through the activation of the hypothalamus pituitary-adrenal (HPA) axis, autonomic and neuroendocrine system with an immediate impact on gut microbiota<sup>[26,27]</sup>. In this regard O'Mahony *et al.*<sup>[28]</sup>, showed that early maternal separation in rats increased corticosterone systemic level, resulting in the alteration of immune response and fecal microbiota. Among several actors of this axis, important molecules have been studied such as vasoactive intestinal peptide (VIP) serotonin, melatonin, gamma-aminobutyric acid (GABA), catecholamines, histamine and acetylcholine<sup>[29-32]</sup>, even if interaction way and acting routes of these molecules is not fully established.

Autism spectrum disorder (ASD) is a range of developmental neuro-behavioral disorders characterized by restricted and repetitive behaviour, impaired social interaction and communication; among these, autism represents the primary type of ASD<sup>[12,16]</sup>.

The possible role of gut microorganism in the pathogenesis of such disorders has been widely deepened by several studies in animal models using different approaches: comparison of gut microbiota composition between affected samples and controls; observation of behaviour changes after administration of gut microbiota modulators in affected subjects rather than virulence factors in controls.

It has been demonstrated that a large amount of species under the *Clostridium* genus (10 times more) characterised the qualitative composition of fecal samples of autistic children<sup>[33-35]</sup>. Then, the composition of microbiota has been characterized, showing an imbalance of *Bacteroidetes* and *Firmicutes* phyla, with an increased presence of *Bacteroidetes* and other gut commensal such as *Bifidobacterium*, *Lactobacillus*, *Sutterella*, *Prevotella*, *Ruminococcus* genera and *Alcaligenaceae* family<sup>[36-40]</sup>.

In the 1998, Bolte<sup>[41]</sup> observed that a significant percentage of individuals with autism had a history

of extensive antibiotic use that significantly disrupt protective intestinal microbiota. On this basis, he outlined the possibility of a subacute, chronic tetanus infection of the intestinal tract that underlies the pathogenesis of symptoms in autism observed in some individuals.

Sandler *et al.*<sup>[42]</sup> speculated that the alteration of autochthonous gut flora microbiota leads to the colonization by bacteria able to produce neurotoxins, contributing, at least in part, to their autistic symptomatology. On this basis, they treated a small group of children affected by regressive-onset autism with poor oral absorption-antibiotic. At the end of treatment, short-term improvement was noted using multiple pre- and post-therapy evaluations.

It has been also studied the consequences of gut barrier alteration contribute to ASD. A study carried on by Emanuele *et al.*<sup>[43]</sup> showed that LPS serum levels were significantly higher in autistic patients compared to health individuals and correlated with socialization scores in an inverse and independent manner. These evidences support a role of microbiota and, generally, of an alteration of the gut barrier in its integrity, in the genesis of ASD.

Nevertheless, the existence of a gastrointestinal dysbiosis as an actor in the ASD etiopathogenesis remains a controversial topic. In this regard, the study carried on by Gondalia *et al.*<sup>[44]</sup> didn't showed clinically meaningful differences in the gut microbiota characterization between children affected by autism and their neurotypical siblings.

Depression is a major form of mood disorder characterized by depressed mood and/or recurrent thoughts of death and/or loss of interest or pleasure in life activities present over a period of at least 2 wk, accompanied by at least five additional symptoms that cause clinically significant impairment in social, work, or other important areas of functioning<sup>[13]</sup>. It results from neuro-psychiatric disturbance, immunological deregulation, genetic factors and environmental influences; nevertheless, a correlation with gut microbiota is emerging<sup>[45-47]</sup>; Through humoral route, microbiota can also influence CNS neurotransmission: it has been demonstrated that in GF mice anxiety-like behavior is reduced and modulated after restoration of the intestinal microbiota<sup>[48-50]</sup>. In particular, administration of *Lactobacillus* sp, *Bifidobacteria* sp, *L. helveticus*, *B. longum*, *L. rhamnosus* and *Lactobacillus farciminis* in murine sample lay to an improvement of depression and anxiety symptoms<sup>[51]</sup>.

In particular, an alteration of intestinal permeability, causing high level of LPS into the bloodstream, lead to the activation of inflammatory and immune response; these processes have been hypothesized as causative factors in psychiatric disorders such as depression<sup>[52,53]</sup>. Moreover, as support to this hypothesis, it has been demonstrated that the administration of LPS in healthy subject is associated to increase of pro-inflammatory cytokines and plasma norepinephrine, whit higher

**Table 1 Alterations of gut microbiota found in autism and mood disorders**

Disease	Microbiota alterations
Autism	Imbalance of <i>Bacteroidetes</i> / <i>Firmicutes</i> ratio Increase of <i>Bacteroidetes</i> phylum, <i>Bifidobacterium</i> , <i>Lactobacillus</i> , <i>Sutterella</i> , <i>Prevotella</i> , <i>Ruminococcus</i> genera, <i>Alcaligenaceae</i> family
Depression	Increase of <i>Alistipes</i> Negative correlation between <i>Faecalibacterium</i> abundance and severity of disease

depression rates<sup>[54]</sup>.

Among clinical studies conducted, gut microbiota has been characterized, showing an overexpression of *Alistipes* in patients affected by depression disorder<sup>[47]</sup>. The overexpression of this bacterium, a genus in the phylum of *Bacteroidetes*, has been demonstrated in other disorders, such as chronic fatigue syndrome and in IBS<sup>[55,56]</sup>. This evidence lead to speculate about a gut microbiota alteration as common mechanism of action in the genesis of these disorders. Moreover, *Alistipes* has been linked to depression mood by generation of inflammatory molecules able to spread into the bloodstream in condition of altered intestinal permeability<sup>[47,51,57]</sup>. Another study, carried on by Jiang *et al*<sup>[58]</sup>, confirmed the overexpression of *Alistipes* in psychiatric disorder and observed a negative correlation between expression of *Faecalibacterium* and the severity of depressive manifestations. An overview of main alterations of gut microbiota in autism and depression is available in Table 1.

## POTENTIAL FOR THERAPEUTICS

### Antibiotics

Antibiotics are the oldest drugs used in the management of diseases of the gastrointestinal tract. Their use, especially for infectious diseases, can achieve an alteration of the composition of the gut microbiota that can lead to significant side effects, not the least of antibiotic-associated diarrhoea due to *Clostridium difficile*<sup>[59]</sup>. Despite this, the antibiotic therapy is currently encouraged in the management of disorders such as IBS, IBD and SIBO in which the modulation of the intestinal flora leading to a net clinical improvement.

Currently, researches are being made in order to clarify the modulation of gut microbiota in the management of psychiatric disorder. It has been demonstrated that reduction of luminal LPS concentration due to antibiotic therapy lead to attenuation of HPA axis stress response and to increase of hypothalamic pro-inflammatory cytokines expression<sup>[60]</sup>.

Desbonnet *et al*<sup>[61]</sup> have reproduced the effect of microbiota depletion on murine specimens: they administered them a combination of antibiotics and then assessed the effects from weaning onwards on adult cognitive, social and emotional behaviours and

markers of gut-brain axis dysfunction in mice. They demonstrated that the reduction and diversity of the gut microbiota influences adult behaviours and key neuromodulators of the gut-brain axis: it reduced anxiety, induced cognitive deficits, altered the brain hormone expression and altered dynamics of the tryptophan metabolic pathway.

In support of these findings, some studies have successfully tested minocycline, second-generation tetracycline, as a treatment for depression, on the basis of its neuroprotective activities and regulation of pro-inflammatory agents<sup>[62,63]</sup>.

In an other study, 11 children affected by ASD have been treated with vancomycin: after the planned 8 wk of treatment, communication and behaviour tests improvement has been observed<sup>[42]</sup>.

Thus, it's possible to speculate that antibiotic treatment, through modulation of gut microbiota, should be able to influences symptoms and expression of psychiatric disorders.

### Probiotics

Probiotics are defined as live micro-organisms, preferentially of human origin, that upon ingestion in specific and sufficient numbers confer non-specific health benefits to the host<sup>[64]</sup>.

Currently widely used in gastrointestinal system disorders, they exert their therapeutic effect by interacting on various levels in the reconstitution of the gastrointestinal barrier. In addition to a direct effect in the composition of Gut Microbiota, they are able to modulate the GI barrier through the increase of mucin production by goblet cells, strengthening the tight junctions and thus the apical intercellular adhesion<sup>[65-68]</sup>.

Probiotics are also involved in the modulation of the immune and inflammatory response by promoting the production of regulatory T cells. They may also regulate the Th1 response, by inhibition the production by the dendritic cells of pro-inflammatory cytokines such as IL-12, TNF- $\alpha$  and INF- $\alpha$ , or increase the expression of anti-inflammatory mediators such as IL-10 and  $\beta$ -TFGF<sup>[67]</sup>.

Some studies tested probiotics as symptoms' modulator in disorders such as anxiety and depression. For example, Bravo *et al*<sup>[69]</sup> demonstrated that chronic administration of *L. rhamnosus* modulates GABA expression in CNS in rat, leading to a reduction in the hippocampus, amygdala, and locus coeruleus and to an increase in cortical regions. Furthermore, it reduces levels of corticosterone induced by stress and depression- and anxiety-related symptoms. In particular, these events didn't appear in vagotomised mice, indicating a fundamental role of vagal sings, and generally of neuronal transmission, in the gut-brain axis.

Similarly, combination of *L. helveticus* and *B. longum* appears to have an anxiolytic-like activity in

rats and, in addition to a diet formulation containing high levels of polyunsaturated fatty acids (PUFAs) n-3, to reduce post-MI depression<sup>[70,71]</sup>.

Despite these impressive results, few clinical trials have been conducted with poor results. A double-blind, randomized clinical trial demonstrated that the daily administration of mixture of probiotics containing *L. helveticus* and *B. longum* for a month reduce psychological distress in healthy controls<sup>[70]</sup>.

Rao *et al*<sup>[72]</sup> showed that the daily administration of *Lactobacillus casei* for two months improves anxiety related symptoms in subject affected by chronic fatigue syndrome<sup>[58]</sup>.

However, the daily assumption of *L. casei* enriched milk didn't show significant effects in term of mood in healthy individuals while seemed to have potentially negative effects on recall memory<sup>[73]</sup>.

Finally, Hsiao *et al*<sup>[74]</sup> showed that the oral administration of *Bacteroides fragilis*, improved some mood symptoms- such as anxiety, stereotypical behaviour and sensorimotor gating-in a maternal immune activation (MIA) animal model that is known to display features of ASD.

### Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) represents the injection of filtrate stools from a healthy donor to a patient for the healing of a specific disease. Despite it had been sporadically used in ancient times, its first application in contemporary medicine in English literature, dates back 1958, when Ben Eiseman infused fecal material in four patients with pseudomembranous colitis<sup>[75]</sup>. After this pioneering experience, several attempts were reported over time for the treatment of *C. difficile* infection. To date, several systematic reviews and meta-analyses<sup>[76-78]</sup>, as well as three randomized controlled trials<sup>[79-81]</sup>, outlined the undoubted efficacy of FMT for the treatment of recurrent *C. difficile* infection. Some proof-of-concept randomized controlled trials investigated the efficacy of FMT in metabolic syndrome<sup>[82]</sup> and IBD, respectively<sup>[83,84]</sup>. In particular, it has been reported that FMT improved sexual function in patients with Crohn's diseases: this finding might get stronger the connection between of gut microbiota and depression/mood<sup>[85]</sup>. At present, despite the theoretical background for the application of FMT to autism is sound, to date it was experienced only in two autistic children, in whom it showed an amelioration of specific symptoms<sup>[86]</sup>.

## CONCLUSION

In the last few years, the importance of gut microbiota in the maintenance of physiological state into the GI system is supported by several studies that have shown a qualitative and quantitative alteration of the intestinal flora in a number of gastrointestinal and extra-gastrointestinal diseases. The application

of gut microbiota modulators, such as probiotics, antibiotics, up to FMT, has been widely experimented as therapeutic instrument for GI diseases with exciting results.

Up to now, available evidences display that the impairment of gut microbiota plays a key role also in the development of autism and mood disorders, but the mechanism through which it does is not fully clear. The application of therapeutic modulators of gut microbiota to autism and mood disorders has been experienced only in experimental settings to date, with few but promising results.

A deeper assessment of the role of intestinal flora in the genesis and development of mood disorders and ASD is currently required; the knowledge advancement of the modulation of the intestinal flora not only about possible modalities but also about the timing in which this should be done, would lead to a new and safe therapeutic weapon in the management of ASD and mood disorders.

## REFERENCES

- 1 **Sartor RB.** Microbial influences in inflammatory bowel diseases. *Gastroenterology* 2008; **134**: 577-594 [PMID: 18242222 DOI: 10.1053/j.gastro.2007.11.059]
- 2 **Schmidt C, Stallmach A.** Etiology and pathogenesis of inflammatory bowel disease. *Minerva Gastroenterol Dietol* 2005; **51**: 127-145 [PMID: 15990703]
- 3 **Eckburg PB, Lepp PW, Relman DA.** Archaea and their potential role in human disease. *Infect Immun* 2003; **71**: 591-596 [PMID: 12540534]
- 4 **Breitbart M, Hewson I, Felts B, Mahaffy JM, Nulton J, Salamon P, Rohwer F.** Metagenomic analyses of an uncultured viral community from human feces. *J Bacteriol* 2003; **185**: 6220-6223 [PMID: 14526037]
- 5 **Burger-van Paassen N, Vincent A, Puiman PJ, van der Sluis M, Bouma J, Boehm G, van Goudoever JB, van Seuning I, Renes IB.** The regulation of intestinal mucin MUC2 expression by short-chain fatty acids: implications for epithelial protection. *Biochem J* 2009; **420**: 211-219 [PMID: 19228118 DOI: 10.1042/BJ20082222]
- 6 **Nell S, Suerbaum S, Josenhans C.** The impact of the microbiota on the pathogenesis of IBD: lessons from mouse infection models. *Nat Rev Microbiol* 2010; **8**: 564-577 [PMID: 20622892 DOI: 10.1038/nrmicro2403]
- 7 **Scaldaferri F, Pizzoferrato M, Gerardi V, Lopetuso L, Gasbarrini A.** The gut barrier: new acquisitions and therapeutic approaches. *J Clin Gastroenterol* 2012; **46** Suppl: S12-S17 [PMID: 22955350 DOI: 10.1097/MCG.0b013e31826ae849]
- 8 **Round JL, O'Connell RM, Mazmanian SK.** Coordination of tolerogenic immune responses by the commensal microbiota. *J Autoimmun* 2010; **34**: J220-J225 [PMID: 19963349 DOI: 10.1016/j.jaut.2009.11.007]
- 9 **Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R.** Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell* 2004; **118**: 229-241 [PMID: 15260992 DOI: 10.1016/j.cell.2004.07.002]
- 10 **Sekirov I, Russell SL, Antunes LC, Finlay BB.** Gut microbiota in health and disease. *Physiol Rev* 2010; **90**: 859-904 [PMID: 20664075 DOI: 10.1152/physrev.00045.2009]
- 11 **Sonnenburg ED, Zheng H, Joglekar P, Higginbottom SK, Firkbank SJ, Bolam DN, Sonnenburg JL.** Specificity of polysaccharide use in intestinal bacteroides species determines diet-induced microbiota alterations. *Cell* 2010; **141**: 1241-1252 [PMID: 20603004 DOI: 10.1016/j.cell.2010.05.005]

- 12 **Fond G**, Boukouaci W, Chevalier G, Regnault A, Eberl G, Hamdani N, Dickerson F, Macgregor A, Boyer L, Dargel A, Oliveira J, Tamouza R, Leboyer M. The “psychomicrobiotic”: Targeting microbiota in major psychiatric disorders: A systematic review. *Pathol Biol (Paris)* 2015; **63**: 35-42 [PMID: 25468489 DOI: 10.1016/j.patbio.2014.10.003]
- 13 **Zhou L**, Foster JA. Psychobiotics and the gut-brain axis: in the pursuit of happiness. *Neuropsychiatr Dis Treat* 2015; **11**: 715-723 [PMID: 25834446 DOI: 10.2147/NDT.S61997]
- 14 **Natividad JM**, Verdu EF. Modulation of intestinal barrier by intestinal microbiota: pathological and therapeutic implications. *Pharmacol Res* 2013; **69**: 42-51 [PMID: 23089410 DOI: 10.1016/j.phrs.2012.10.007]
- 15 **de Silva HJ**, Millard PR, Soper N, Kettlewell M, Mortensen N, Jewell DP. Effects of the faecal stream and stasis on the ileal pouch mucosa. *Gut* 1991; **32**: 1166-1169 [PMID: 1955172]
- 16 **Wang Y**, Kasper LH. The role of microbiome in central nervous system disorders. *Brain Behav Immun* 2014; **38**: 1-12 [PMID: 24370461 DOI: 10.1016/j.bbi.2013.12.015]
- 17 **Dinan TG**, Cryan JF. The impact of gut microbiota on brain and behaviour: implications for psychiatry. *Curr Opin Clin Nutr Metab Care* 2015; **18**: 552-558 [PMID: 26372511 DOI: 10.1097/MCO.0000000000000221]
- 18 **Collins SM**, Surette M, Bercik P. The interplay between the intestinal microbiota and the brain. *Nat Rev Microbiol* 2012; **10**: 735-742 [PMID: 23000955 DOI: 10.1038/nrmicro2876]
- 19 **Müller N**, Myint AM, Schwarz MJ. Inflammation in schizophrenia. *Adv Protein Chem Struct Biol* 2012; **88**: 49-68 [PMID: 22814706 DOI: 10.1016/B978-0-12-398314-5.00003-9]
- 20 **Miller AH**, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry* 2009; **65**: 732-741 [PMID: 19150053 DOI: 10.1016/j.biopsych.2008.11.029]
- 21 **Berk M**, Kapczynski F, Andreazza AC, Dean OM, Giorlando F, Maes M, Yücel M, Gama CS, Dodd S, Dean B, Magalhães PV, Amminger P, McGorry P, Malhi GS. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci Biobehav Rev* 2011; **35**: 804-817 [PMID: 20934453 DOI: 10.1016/j.neubiorev.2010.10.001]
- 22 **O'Malley D**, Quigley EM, Dinan TG, Cryan JF. Do interactions between stress and immune responses lead to symptom exacerbations in irritable bowel syndrome? *Brain Behav Immun* 2011; **25**: 1333-1341 [PMID: 21536124 DOI: 10.1016/j.bbi.2011.04.009]
- 23 **Castro-Nallar E**, Bendall ML, Pérez-Losada M, Sabuncyan S, Severance EG, Dickerson FB, Schroeder JR, Yolken RH, Crandall KA. Composition, taxonomy and functional diversity of the oropharynx microbiome in individuals with schizophrenia and controls. *PeerJ* 2015; **3**: e1140 [PMID: 26336637 DOI: 10.7717/peerj.1140]
- 24 **Haba R**, Shintani N, Onaka Y, Wang H, Takenaga R, Hayata A, Baba A, Hashimoto H. Lipopolysaccharide affects exploratory behaviors toward novel objects by impairing cognition and/or motivation in mice: Possible role of activation of the central amygdala. *Behav Brain Res* 2012; **228**: 423-431 [PMID: 22209851 DOI: 10.1016/j.bbr.2011.12.027]
- 25 **Kastin AJ**, Pan W. Concepts for biologically active peptides. *Curr Pharm Des* 2010; **16**: 3390-3400 [PMID: 20726835]
- 26 **Rhee SH**, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain-gut-enteric microbiota axis. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 306-314 [PMID: 19404271 DOI: 10.1038/nrgastro.2009.35]
- 27 **Cryan JF**, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci* 2012; **13**: 701-712 [PMID: 22968153 DOI: 10.1038/nrn3346]
- 28 **O'Mahony SM**, Marchesi JR, Scully P, Codling C, Ceolho AM, Quigley EM, Cryan JF, Dinan TG. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. *Biol Psychiatry* 2009; **65**: 263-267 [PMID: 18723164 DOI: 10.1016/j.biopsych.2008.06.026]
- 29 **Barrett E**, Ross RP, O'Toole PW, Fitzgerald GF, Stanton C.  $\gamma$ -Aminobutyric acid production by culturable bacteria from the human intestine. *J Appl Microbiol* 2012; **113**: 411-417 [PMID: 22612585 DOI: 10.1111/j.1365-2672.2012.05344.x]
- 30 **Forsythe P**, Sudo N, Dinan T, Taylor VH, Bienenstock J. Mood and gut feelings. *Brain Behav Immun* 2010; **24**: 9-16 [PMID: 19481599 DOI: 10.1016/j.bbi.2009.05.058]
- 31 **Lyte M**. Probiotics function mechanistically as delivery vehicles for neuroactive compounds: Microbial endocrinology in the design and use of probiotics. *Bioessays* 2011; **33**: 574-581 [PMID: 21732396 DOI: 10.1002/bies.201100024]
- 32 **Velickovic K**, Markelic M, Golic I, Otasevic V, Stancic A, Jankovic A, Vucetic M, Buzadzic B, Korac B, Korac A. Long-term dietary L-arginine supplementation increases endothelial nitric oxide synthase and vasoactive intestinal peptide immunoreexpression in rat small intestine. *Eur J Nutr* 2014; **53**: 813-821 [PMID: 24100601 DOI: 10.1007/s00394-013-0585-8]
- 33 **Finegold SM**, Molitoris D, Song Y, Liu C, Vaisanen ML, Bolte E, McTeague M, Sandler R, Wexler H, Marlowe EM, Collins MD, Lawson PA, Summanen P, Baysallar M, Tomzynski TJ, Read E, Johnson E, Rolfé R, Nasir P, Shah H, Haake DA, Manning P, Kaul A. Gastrointestinal microflora studies in late-onset autism. *Clin Infect Dis* 2002; **35**: S6-S16 [PMID: 12173102 DOI: 10.1086/341914]
- 34 **Song Y**, Liu C, Finegold SM. Real-time PCR quantitation of clostridia in feces of autistic children. *Appl Environ Microbiol* 2004; **70**: 6459-6465 [PMID: 15528506 DOI: 10.1128/AEM.70.11.6459-6465.2004]
- 35 **Parracho HM**, Bingham MO, Gibson GR, McCartney AL. Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. *J Med Microbiol* 2005; **54**: 987-991 [PMID: 16157555 DOI: 10.1099/jmm.0.46101-0]
- 36 **Finegold SM**, Dowd SE, Gontcharova V, Liu C, Henley KE, Wolcott RD, Youn E, Summanen PH, Granpeesheh D, Dixon D, Liu M, Molitoris DR, Green JA. Pyrosequencing study of fecal microflora of autistic and control children. *Anaerobe* 2010; **16**: 444-453 [PMID: 20603222 DOI: 10.1016/j.anaerobe.2010.06.008]
- 37 **Adams JB**, Johansen LJ, Powell LD, Quig D, Rubin RA. Gastrointestinal flora and gastrointestinal status in children with autism--comparisons to typical children and correlation with autism severity. *BMC Gastroenterol* 2011; **11**: 22 [PMID: 21410934 DOI: 10.1186/1471-230X-11-22]
- 38 **Kang DW**, Park JG, Ilhan ZE, Wallstrom G, Labaer J, Adams JB, Krajmalnik-Brown R. Reduced incidence of Prevotella and other fermenters in intestinal microflora of autistic children. *PLoS One* 2013; **8**: e68322 [PMID: 23844187 DOI: 10.1371/journal.pone.0068322]
- 39 **Wang L**, Christophersen CT, Sorich MJ, Gerber JP, Angley MT, Conlon MA. Increased abundance of Sutterella spp. and Ruminococcus torques in feces of children with autism spectrum disorder. *Mol Autism* 2013; **4**: 42 [PMID: 24188502 DOI: 10.1186/2040-2392-4-42]
- 40 **Williams BL**, Hornig M, Parekh T, Lipkin WI. Application of novel PCR-based methods for detection, quantitation, and phylogenetic characterization of Sutterella species in intestinal biopsy samples from children with autism and gastrointestinal disturbances. *MBio* 2012; **3**: pii: e00261-11 [PMID: 22233678 DOI: 10.1128/mBio.00261-11]
- 41 **Bolte ER**. Autism and Clostridium tetani. *Med Hypotheses* 1998; **51**: 133-144 [PMID: 9881820]
- 42 **Sandler RH**, Finegold SM, Bolte ER, Buchanan CP, Maxwell AP, Väisänen ML, Nelson MN, Wexler HM. Short-term benefit from oral vancomycin treatment of regressive-onset autism. *J Child Neurol* 2000; **15**: 429-435 [PMID: 10921511]
- 43 **Emanuele E**, Orsi P, Boso M, Broglia D, Brondino N, Barale F, di Nemi SU, Politi P. Low-grade endotoxemia in patients with severe autism. *Neurosci Lett* 2010; **471**: 162-165 [PMID: 20097267 DOI: 10.1016/j.neulet.2010.01.033]
- 44 **Gondalia SV**, Palombo EA, Knowles SR, Cox SB, Meyer D, Austin DW. Molecular characterisation of gastrointestinal microbiota of children with autism (with and without gastrointestinal dysfunction) and their neurotypical siblings. *Autism Res* 2012; **5**: 419-427 [PMID:

- 22997101 DOI: 10.1002/aur.1253]
- 45 **Dash S**, Clarke G, Berk M, Jacka FN. The gut microbiome and diet in psychiatry: focus on depression. *Curr Opin Psychiatry* 2015; **28**: 1-6 [PMID: 25415497 DOI: 10.1097/YCO.000000000000117]
- 46 **Dantzer R**, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008; **9**: 46-56 [PMID: 18073775 DOI: 10.1038/nrn2297]
- 47 **Naseribafrouei A**, Hestad K, Avershina E, Sekelja M, Linlökken A, Wilson R, Rudi K. Correlation between the human fecal microbiota and depression. *Neurogastroenterol Motil* 2014; **26**: 1155-1162 [PMID: 24888394 DOI: 10.1111/nmo.12378]
- 48 **Neufeld KM**, Kang N, Bienenstock J, Foster JA. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterol Motil* 2011; **23**: 255-264, e119 [PMID: 21054680 DOI: 10.1111/j.1365-2982.2010.01620.x]
- 49 **Clarke G**, Grenham S, Scully P, Fitzgerald P, Moloney RD, Shanahan F, Dinan TG, Cryan JF. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Mol Psychiatry* 2013; **18**: 666-673 [PMID: 22688187 DOI: 10.1038/mp.2012.77]
- 50 **Logan AC**, Katzman M. Major depressive disorder: probiotics may be an adjuvant therapy. *Med Hypotheses* 2005; **64**: 533-538 [PMID: 15617861 DOI: 10.1016/j.mehy.2004.08.019]
- 51 **Luna RA**, Foster JA. Gut brain axis: diet microbiota interactions and implications for modulation of anxiety and depression. *Curr Opin Biotechnol* 2015; **32**: 35-41 [PMID: 25448230 DOI: 10.1016/j.copbio.2014.10.007]
- 52 **Qin L**, Wu X, Block ML, Liu Y, Breese GR, Hong JS, Knapp DJ, Crews FT. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia* 2007; **55**: 453-462 [PMID: 17203472 DOI: 10.1002/glia.20467]
- 53 **Berk M**, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML, Maes M. So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med* 2013; **11**: 200 [PMID: 24228900 DOI: 10.1186/1741-7015-11-200]
- 54 **Grigoleit JS**, Kullmann JS, Wolf OT, Hammes F, Wegner A, Jablonowski S, Engler H, Gizewski E, Oberbeck R, Schedlowski M. Dose-dependent effects of endotoxin on neurobehavioral functions in humans. *PLoS One* 2011; **6**: e28330 [PMID: 22164271 DOI: 10.1371/journal.pone.0028330]
- 55 **Frémont M**, Coomans D, Massart S, De Meirleir K. High-throughput 16S rRNA gene sequencing reveals alterations of intestinal microbiota in myalgic encephalomyelitis/chronic fatigue syndrome patients. *Anaerobe* 2013; **22**: 50-56 [PMID: 23791918 DOI: 10.1016/j.anaerobe.2013.06.002]
- 56 **Saulnier DM**, Riehle K, Mistretta TA, Diaz MA, Mandal D, Raza S, Weidler EM, Qin X, Coarfa C, Milosavljevic A, Petrosino JF, Highlander S, Gibbs R, Lynch SV, Shulman RJ, Versalovic J. Gastrointestinal microbiome signatures of pediatric patients with irritable bowel syndrome. *Gastroenterology* 2011; **141**: 1782-1791 [PMID: 21741921 DOI: 10.1053/j.gastro.2011.06.072]
- 57 **Bangsgaard Bendtsen KM**, Krych L, Sørensen DB, Pang W, Nielsen DS, Josefsen K, Hansen LH, Sørensen SJ, Hansen AK. Gut microbiota composition is correlated to grid floor induced stress and behavior in the BALB/c mouse. *PLoS One* 2012; **7**: e46231 [PMID: 23056268 DOI: 10.1371/journal.pone.0046231]
- 58 **Jiang H**, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y, Wang W, Tang W, Tan Z, Shi J, Li L, Ruan B. Altered fecal microbiota composition in patients with major depressive disorder. *Brain Behav Immun* 2015; **48**: 186-194 [PMID: 25882912 DOI: 10.1016/j.bbi.2015.03.016]
- 59 **Khanna S**, Pardi DS. The growing incidence and severity of *Clostridium difficile* infection in inpatient and outpatient settings. *Expert Rev Gastroenterol Hepatol* 2010; **4**: 409-416 [PMID: 20678014 DOI: 10.1586/egh.10.48]
- 60 **Ait-Belgnaoui A**, Durand H, Cartier C, Chaumaz G, Eutamene H, Ferrier L, Houdeau E, Fioramonti J, Bueno L, Theodorou V. Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology* 2012; **37**: 1885-1895 [PMID: 22541937 DOI: 10.1016/j.psyneuen.2012.03.024]
- 61 **Desbonnet L**, Clarke G, Traplin A, O'Sullivan O, Crispie F, Moloney RD, Cotter PD, Dinan TG, Cryan JF. Gut microbiota depletion from early adolescence in mice: Implications for brain and behaviour. *Brain Behav Immun* 2015; **48**: 165-173 [PMID: 25866195 DOI: 10.1016/j.bbi.2015.04.004]
- 62 **Soczynska JK**, Mansur RB, Brietzke E, Swardfager W, Kennedy SH, Woldeyohannes HO, Powell AM, Manierka MS, McIntyre RS. Novel therapeutic targets in depression: minocycline as a candidate treatment. *Behav Brain Res* 2012; **235**: 302-317 [PMID: 22963995 DOI: 10.1016/j.bbr.2012.07.026]
- 63 **Miyaoka T**, Wake R, Furuya M, Liaury K, Ieda M, Kawakami K, Tsuchie K, Taki M, Ishihara K, Araki T, Horiguchi J. Minocycline as adjunctive therapy for patients with unipolar psychotic depression: an open-label study. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; **37**: 222-226 [PMID: 22349578 DOI: 10.1016/j.pnpbp.2012.02.002]
- 64 **Caselli M**, Cassol F, Calò G, Holton J, Zuliani G, Gasbarrini A. Actual concept of "probiotics": is it more functional to science or business? *World J Gastroenterol* 2013; **19**: 1527-1540 [PMID: 23539674 DOI: 10.3748/wjg.v19.i10.1527]
- 65 **Scaldaferri F**, Pizzoferrato M, Pecere S, Forte F, Gasbarrini A. Bacterial flora as a cause or treatment of chronic diarrhea. *Gastroenterol Clin North Am* 2012; **41**: 581-602 [PMID: 22917165 DOI: 10.1016/j.gtc.2012.06.002]
- 66 **Gareau MG**, Sherman PM, Walker WA. Probiotics and the gut microbiota in intestinal health and disease. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 503-514 [PMID: 20664519 DOI: 10.1038/nrgastro.2010.117]
- 67 **Ng SC**, Hart AL, Kamm MA, Stagg AJ, Knight SC. Mechanisms of action of probiotics: recent advances. *Inflamm Bowel Dis* 2009; **15**: 300-310 [PMID: 18626975 DOI: 10.1002/ibd.20602]
- 68 **Otte JM**, Podolsky DK. Functional modulation of enterocytes by gram-positive and gram-negative microorganisms. *Am J Physiol Gastrointest Liver Physiol* 2004; **286**: G613-G626 [PMID: 15010363 DOI: 10.1152/ajpgi.00341.2003]
- 69 **Bravo JA**, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci USA* 2011; **108**: 16050-16055 [PMID: 21876150 DOI: 10.1073/pnas.1102999108]
- 70 **Messaoudi M**, Lalonde R, Violle N, Javelot H, Desor D, Nejd A, Bisson JF, Rougeot C, Pichelin M, Cazaubiel M, Cazaubiel JM. Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in rats and human subjects. *Br J Nutr* 2011; **105**: 755-764 [PMID: 20974015 DOI: 10.1017/S0007114510004319]
- 71 **Gilbert K**, Arseneault-Bréard J, Flores Monaco F, Beaudoin A, Bah TM, Tompkins TA, Godbout R, Rousseau G. Attenuation of post-myocardial infarction depression in rats by n-3 fatty acids or probiotics starting after the onset of reperfusion. *Br J Nutr* 2013; **109**: 50-56 [PMID: 23068715 DOI: 10.1017/S0007114512003807]
- 72 **Rao AV**, Bsted AC, Beaulne TM, Katzman MA, Iorio C, Berardi JM, Logan AC. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathog* 2009; **1**: 6 [PMID: 19338686 DOI: 10.1186/1757-4749-1-6]
- 73 **Benton D**, Williams C, Brown A. Impact of consuming a milk drink containing a probiotic on mood and cognition. *Eur J Clin Nutr* 2007; **61**: 355-361 [PMID: 17151594 DOI: 10.1038/sj.ejcn.1602546]
- 74 **Hsiao EY**, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, Patterson PH, Mazmanian SK. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* 2013; **155**: 1451-1463 [PMID: 24315484 DOI: 10.1016/j.cell.2013.11.024]
- 75 **Eiseman B**, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. *Surgery*

- 1958; **44**: 854-859 [PMID: 13592638]
- 76 **Cammarota G**, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of *Clostridium difficile* infection: a systematic review. *J Clin Gastroenterol* 2014; **48**: 693-702 [PMID: 24440934 DOI: 10.1097/MCG.0000000000000046]
- 77 **Kassam Z**, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. *Am J Gastroenterol* 2013; **108**: 500-508 [PMID: 23511459 DOI: 10.1038/ajg.2013.59]
- 78 **Drekonja D**, Reich J, Gezahegn S, Greer N, Shaukat A, MacDonald R, Rutks I, Wilt TJ. Fecal Microbiota Transplantation for *Clostridium difficile* Infection: A Systematic Review. *Ann Intern Med* 2015; **162**: 630-638 [PMID: 25938992 DOI: 10.7326/M14-2693]
- 79 **van Nood E**, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, Speelman P, Dijkgraaf MG, Keller JJ. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013; **368**: 407-415 [PMID: 23323867 DOI: 10.1056/NEJMoa1205037]
- 80 **Cammarota G**, Masucci L, Ianiro G, Bibbò S, Dinio G, Costamagna G, Sanguinetti M, Gasbarrini A. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection. *Aliment Pharmacol Ther* 2015; **41**: 835-843 [PMID: 25728808 DOI: 10.1111/apt.13144]
- 81 **Youngster I**, Sauk J, Pindar C, Wilson RG, Kaplan JL, Smith MB, Alm EJ, Gevers D, Russell GH, Hohmann EL. Fecal microbiota transplant for relapsing *Clostridium difficile* infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. *Clin Infect Dis* 2014; **58**: 1515-1522 [PMID: 24762631 DOI: 10.1093/cid/ciu135]
- 82 **Vrieze A**, Van Nood E, Holleman F, Salojärvi J, Kootte RS, Bartelsman JF, Dallinga-Thie GM, Ackermans MT, Serlie MJ, Oozeer R, Derrien M, Druesne A, Van Hylckama Vlieg JE, Bloks VW, Groen AK, Heilig HG, Zoetendal EG, Strees ES, de Vos WM, Hoekstra JB, Nieuwdorp M. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 2012; **143**: 913-916.e7 [PMID: 22728514 DOI: 10.1053/j.gastro.2012.06.031]
- 83 **Moayyedi P**, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, Armstrong D, Marshall JK, Kassam Z, Reinisch W, Lee CH. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. *Gastroenterology* 2015; **149**: 102-109.e6 [PMID: 25857665 DOI: 10.1053/j.gastro.2015.04.001]
- 84 **Rossen NG**, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflou A, Löwenberg M, van den Brink GR, Mathus-Vliegen EM, de Vos WM, Zoetendal EG, D'Haens GR, Ponsioen CY. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. *Gastroenterology* 2015; **149**: 110-118.e4 [PMID: 25836986 DOI: 10.1053/j.gastro.2015.03.045]
- 85 **Cui B**, Feng Q, Wang H, Wang M, Peng Z, Li P, Huang G, Liu Z, Wu P, Fan Z, Ji G, Wang X, Wu K, Fan D, Zhang F. Fecal microbiota transplantation through mid-gut for refractory Crohn's disease: safety, feasibility, and efficacy trial results. *J Gastroenterol Hepatol* 2015; **30**: 51-58 [PMID: 25168749 DOI: 10.1111/jgh.12727]
- 86 **Aroniadis OC**, Brandt LJ. Fecal microbiota transplantation: past, present and future. *Curr Opin Gastroenterol* 2013; **29**: 79-84 [PMID: 23041678 DOI: 10.1097/MOG.0b013e32835a4b3e]

**P- Reviewer:** Nakamura S, Zhang FM **S- Editor:** Qi Y  
**L- Editor:** A **E- Editor:** Wang CH







Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: [bpgooffice@wjgnet.com](mailto:bpgooffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



ISSN 1007-9327

