World Journal of Clinical Cases

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.12998/wjcc.v3.i2.156

World J Clin Cases 2015 February 16; 3(2): 156-162
ISSN 2307-8960 (online)

MINIREVIEWS

Review on microbiota and effectiveness of probiotics use in older

Mariangela Rondanelli, Attilio Giacosa, Milena Anna Faliva, Simone Perna, Francesca Allieri, Anna Maria Castellazzi

Mariangela Rondanelli, Milena Anna Faliva, Simone Perna, Francesca Allieri, Department of Applied Health Sciences, Azienda di Servizi alla Persona di Pavia, University of Pavia, 27100 Pavia, Italy
Mariangela Rondanelli, Department of Public Health, Experimental and Forensic Medicine, School of Medicine, University of Pavia, Azienda di Servizi alla Persona di Pavia, Pavia 27100, Italy
Attilio Giacosa, Department of Gastroenterology, Policlinico di Monza, 20900 Monza, Italy
Anna Maria Castellazzi, Department of Clinical-Surgical, Diagnostic and Pediatrics Sciences, University of Pavia, 27100 Pavia, Italy
Author contributions: Rondanelli M, Giacosa A and Castellazzi AM designed research; Faliva MA, Perna S and Allieri F performed research; Rondanelli M, Giacosa A and Castellazzi AM analyzed data; Rondanelli M wrote the paper.

Correspondence to: Mariangela Rondanelli, Professor, Department of Public Health, Experimental and Forensic Medicine, School of Medicine, University of Pavia, Azienda di Servizi alla Persona di Pavia, Pavia 27100, Italy. mariangela.rondanelli@unipv.it
Telephone: +39-382-381749
Fax: +39-382-381218
Received: July 27, 2014
Peer-review started: July 28, 2014
First decision: September 16, 2014
Revised: October 9, 2014
Accepted: October 28, 2014
Article in press: October 29, 2014
Published online: February 16, 2015

Abstract

The aim of the present systematic review is to summarize the existing knowledge about the human microbiota in the elderly and the effects of probiotics in elderly population. The elderly subjects, compared to adult population, show a reduction in the diversity of the microbiota, characterized by a large interindividual variability, with lower numbers of *Firmicutes*, *Bifidobacteria*, *Clostridium cluster* XIV, *Faecalibacterium Prausnitzii*, *Blautia coccoides-Eubacterium rectal* and higher presence of *Enterobacteriaceae* and *Bacteroidetes*. These differences of the intestinal microbiota of the elderly may not necessarily be caused by aging, but they could be associated with the decline of the general state of health with malnutrition and with increased need for medication, such as antibiotics and nonsteroidal anti-inflammatory drugs, situations that occur frequently in the elderly. Differences have been demonstrated in the composition of the microbiota between healthy elderly subjects and hospitalized or institutionalized elderly subjects. These findings which further indicates that the living conditions, health status, nutrition and drugs have a significant effect on the composition of the microbiota. According to the available knowledge, the use of probiotics is safe and could represent an useful intervention to prevent or treat antibiotic-associated diarrhea, in addition to reducing the severity of symptoms, other than to help the management of constipation.

Key words: Microbiota; Elderly; Probiotics; Antibiotic-associated diarrhea; Constipation

Core tip: The intestinal microbiota of elderly manifested a reduction in the diversity, characterized by a large interindividual variability, with lower numbers of *Firmicutes*, *Bifidobacteria*, *Clostridium cluster* XIV, *Faecalibacterium Prausnitzii*, *Blautia coccoides-Eubacterium rectal* and higher in *Enterobacteriaceae* and *Bacteroidetes*. These derangements may not necessarily

aging-correlated, but they can be consequent to the decline of general state of health, malnutrition and increased use of drugs. As regards probiotics, the main double-blind studies in the elderly have shown that use is safe and could represent an interesting support to reduced frequency and/or duration of antibiotic-associated diarrhea, other than to help for constipation.

Rondanelli M, Giacosa A, Faliva MA, Perna S, Allieri F, Castellazzi AM. Review on microbiota and effectiveness of probiotics use in older. *World J Clin Cases* 2015; 3(2): 156-162 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i2/156.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i2.156

INTRODUCTION

Differences in the composition of the microbiota have been shown in the literature, when healthy elderly and adult have been compared, but differences in the composition of the microbiota have been also shown when healthy elderly and hospitalized or institutionalized elderly patients have been compared. Then, the topic concerning the changes in the composition of the microbiota with age is much debated in the literature. Another issue of great interest is whether the use of probiotics may be effective in the elderly population.

Given this background, the aim of the present review is to summarize the state of the art according to the extant literature about two topics: the changes in the microbiota associated with aging and the activity of probiotics on the microbiota in this age group evaluated with two issues: (1) the effect on the composition of the microbiota after administration of probiotics; and (2) the efficacy of intake of probiotics on symptoms of major gastrointestinal diseases, including the iatrogenic ones, that frequently affect elderly subjects, including constipation, diarrhea secondary to the intake of antibiotics, particularly when linked to the presence of *Clostridium difficile*.

RESEARCH

The present systematic review was performed following the steps by Egger *et al*[1] as follows: configuration of a working group: three operators skilled in clinical nutrition in the geriatric age, of whom one acting as a methodological operator and two participating as clinical operators. Formulation of the revision question on the basis of considerations made in the abstract: "microbiota in elderly, use of probiotics during aging". Identification of relevant studies: a research strategy was planned, on PubMed [Public MedIine run by the National Center of Biotechnology Information (NCBI) of the National Library of Medicine of Bathesda (United States)], as follows: (1) definition of the key words (microbiota, elderly, probiotics), allowing the definition of the interest field of the documents to be searched, grouped in inverted commas ("…") and used separately or in combination; (2) use of: the Boolean AND Operator, that allows the establishments of logical relations among concepts; (3) research modalities: advanced search; (4) limits: time limits: papers published in the last 20 years; humans; languages: English; and (5) manual search performed by the senior researchers experienced in clinical nutrition through the revision of reviews and individual articles on microbiota in elderly published in journals qualified in the Index Medicus. Analysis and presentation of the outcomes: the data extrapolated from the revised studies were collocated in tables; in particular, for each study we specified: the author, the name of the journal where the study was published and year of publication, study characteristics. The analysis was carried out in the form of a narrative review of the reports.

MICROBIOTA IN ELDERLY POPULATION

This research has been carried out based on the following keywords: "microbiota" AND "elderly"; 1040 articles were found. Among them, 6 case control studies, 1 Randomized Controlled Trial (RCT), 6 cross sectional researches, 5 observational studies, 6 reviews, 1 prospective and 1 population based studies have been selected and discussed.

The changes in the microbiota associated with aging are still far from being clarified with certainty, but there are numerous studies that suggest that aging has a significant effect on the microbiota.

First of all, it has to be taken into account that changes in the intestinal microbiota of the elderly may not necessarily be caused by aging: they can be influenced by the decline of the general state of health, by malnutrition and increased need for medication, such as antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs)[2,3], that occur frequently in the elderly. Differences in the composition of the microbiota have been shown when healthy elderly and hospitalized or institutionalized elderly patients have been compared[4,5], thus proving that the living conditions, health status, nutrition and drugs have a significant effect on the composition of the microbiota.

Moreover, the colonic transit has a great influence on the function of the large bowel and increased transit time is related to a reduced fecal bacterial cell mass[6]. Due to a lack of exercise and long periods of bed rest[7,8], intestinal transit times are often significantly increased in hospitalized elderly patients[7], and this may be a factor influencing the changes in the intestinal microbiota in hospitalized or institutionalized elderly compared to healthy

subjects. Moreover, modified diets, parenteral and enteral artificial nutrition and different eating habits during hospitalization[9] may contribute to these variations.

The normal intestinal microbiota provides an important natural defence mechanism against invading pathogens and prevents the overgrowth of opportunistic microorganisms (colonization resistance). Therefore, alterations in the composition of the microbiota that occur in the elderly may lead to negative consequences, such as a decreased efficacy of in the immune system and a higher incidence of gastrointestinal infections, which is more frequent in the elderly than in the young[10]. The immunological changes associated with aging involve reductions of efficiency of the responses mediated by B and T cells[11]. In addition, the increase of circulating antibodies against commensal intestinal bacteria in the elderly has been associated with age-related changes, such as the reduction of gastric acid secretion and increased mucosal permeability[12].

The elderly subjects, compared to the young adult population, show a reduction in the diversity of the microbiota[13], characterized by a large interindividual variability, with a lower number of Bifidobacteria and a higher number of Enterobacteriaceae[14,15]. In addition, the *Bacteroidetes* are more numerous, while the *Firmicutes* appear to be fewer than in the elderly compared to younger adult controls[16]. The elderly population also shows decreased levels of *Clostridium cluster* XIV and *Faecalibacterium Prausnitzii*, which are known as major producers of butyrate[17,18]. Moreover, the levels of *Blautia coccoides - Eubacterium rectal* (formerly known as *Clostridium coccoides - E. Rectale*) are lower in the elderly than in adults[19]. Finally, aging has been associated with an increase in the diversity of species not yet identified[20]. In an interesting recent study[21], a cohort of 178 (non on antibiotic treatment) elderly subjects (mean age 78, range 64-102 years) were recruited by taking into account their place of residence (a group of healthy elderly were resident in a community and a group of frail elderly institutionalized in a long-term care center) and were compared with 13 young adults (mean age 36 years, range 28-46 years), who were used as a control group. The data were acquired through the reading of more than 5 million sequences generated from 16S rRNA amplicons of the gene. The results revealed that the composition of the intestinal microbiota of the elderly considered in the study was correlated with the place where they live. The elderly community residents had a greater number of *Firmicutes* and lower incidence of *Bacteroidetes* when compared the long-term care residents. Considering the division according to the enterotype, six co-abundance groups were detected. The dominant genera were *Bacteroides, Prevotella, Ruminococcus, Oscillibacter, Alistipes* and *CAG Odoribacter*. The transition from healthy elderly living in the community to elderly and frail institutionalized in a long-term care center is accompanied by the dominance of a CAG distinctive, with a significantly greater number of *Prevotella* and *Ruminococcus CAG* in the cohort residing in the community and *Alistipes* and *CAG Oscillibacter* in the cohort of elderly subjects institutionalized in a long-term care center. This study also demonstrated a correlation between alterations of the microbiota and the state of fragility of the elderly, confirming the results of previous study[22]. In addition, the study demonstrated a correlation with increased inflammation (as assessed by the determination of C-reactive protein and interleukin 6 and 8), thus confirming the hypothesis that there is a close association between the presence of the so-called "inflammaging" and alterations of the microbiota[23]. Finally, a clear association between diet and microbiota has been outlined in this study: thus confirms the results of many other studies[24-26].

A recent study by Biagi *et al*[15] evaluated, by means of "Human Intestinal Tract Chip" and quantitative PCR of the 16S rRNA genes of Bacteria and Archaea, the microbiota of centenarians and compared these data with the microbiota of young and not centenarians elderly subjects. The results show that *Firmicutes* and *Bacteroidetes* dominate the intestinal microbiota of centenarians (representing over 93% of total bacteria). Compared to adults and centenarians, in pre centenarian elderly subjects changes were observed in the relative proportion of specific subgroups of *Firmicutes*. A decrease in the contribution of *Clostridium cluster* XIV, an increase in Bacilli, and a rearrangement of *Clostridium cluster* IV, and of *Clostridium cluster* XIVa were found. *Clostridium cluster* XIVa is one of the main bacteria that produce methane, a short chain fatty acid, which is a source of energy for the enterocytes and has been implicated in the protection against intestinal inflammatory diseases. A lower number of several producers of butyrate was observed in centenarians when compared with other age groups, including *Ruminococcus obeum et rel*, *Roseburia intestinalis et rel*, *E. ventriosum et rel*., *E. rectale et rel*., *E. hallii et rel.* (all belonging to the *Clostridium cluster* XIV), and *Papillibacter cinnamovorans et rel*., and *F. Prausnitzii et rel*. (*Clostridium cluster* IV). Conversely, other butyrate producers, such as *Anaerotruncus colihominis et rel*. (*Clostridium cluster* IV), and *Eubacterium limosum et rel*. (*Clostridium cluster* XV) were increased in centenarians. The increase of *E. limosum* is high (about 15 times), and may indicate a group of bacteria characteristic of centenarians. Also the decrease of *F. prausnitzii* in centenarians is of interest, as this species is known to affect inflammation of the intestine. Finally, the intestinal microbiota of centenarians is more

rich in proteobacteria, a group containing many of those bacteria recently defined as "patobionti". These are considered minor and opportunistic components of human intestinal ecosystem that, in some circumstances (for example in the presence of inflammation) can get out of control and cause a disease.

Many therapeutic substances frequently taken by elderly subject[27], such as NSAIDs, are associated with alterations in the microbiota[3]. Mäkivuokko, thanks to the sequencing of the 16S rDNA, demonstrated in a group of 18 elderly people taking NSAIDs, that there are changes in all the major microbial phyla, such as a lower number of *Firmicutes* and an increase number of *Bacteroidetes*. In addition, it was reported a reduction in the number of the known butyrate producers belonging to *Clostridium cluster* XIV, as *Roseburia* and *Ruminococcus*, and, in the *Actinobacteria* cluster, a lower number of *Collinsella* spp. compared to both the young adults and the elderly subjects not taking NSAIDs.

EFFECTIVENESS OF THE USE OF PROBIOTICS IN THE ELDERLY POPULATION

The studies carried out in the elderly population to test the activity of probiotics on the microbiota in this age group, has been evaluated with two topics: the effect on the composition of the microbiota after administration of probiotics; the efficacy of intake of probiotics on symptoms of major gastrointestinal diseases, including the iatrogenic ones, that frequently affect elderly subjects, including constipation, diarrhea secondary to the intake of antibiotics, particularly when linked to the presence of *Clostridium difficile*.

This research has been carried out based on the keywords: "probiotics" AND "elderly" AND "aging"; 56 articles were sourced. Among them, as far as variations in the composition of the microbiota in the elderly after use of probiotics are concerned, 3 randomized double blind clinical trials and 1 observational research have been selected and discussed. Concerning the efficacy of use of probiotics on symptoms of major diseases that affect the elderly, 2 RCT, 7 double blind studies, 3 reviews and 1 cross sectional research have been selected and discussed.

Variations in the composition of the microbiota in elderly after use of probiotics

Regarding changes in the composition of the microbiota following the intake of probiotics, in the elderly population, three double-blind studies versus placebo were selected: (1) the study of Lahtinen *et al*[28] that considered the effect of a fermented oat beverage containing 10^9 cfu/mL *Bifidobacterium longum* 46 (DSM 14583) and *B. longum* 2C (DSM 14579) given daily for 6 mo; (2) the study by Ahmed *et al*[29] that considered the effect of a drink made of reconstituted skim milk containing 3 different doses (5 x 10^9 CFU/die, 1.0 x 10^9 CFU/die and 6.5 x 10^7 CFU/die) of *Bifidobacterium lactis* HN019 (DR10TM) administered daily for 4 wk; and (3) the study of Bartosch *et al*[4] that considered the effect of *Bifidobacterium bifidum* and *B. lactis* in combination with inulin.

Table 1 shows the changes in the composition of the microbiota of the treated group when compared to the placebo group.

Efficacy of use of probiotics on symptoms of major diseases, including iatrogenic, that affect the elderly

In a large controlled study conducted in 360 subjects older than 60 years, the effect of a 3-wk intervention of a fermented milk containing cultures of yogurt and the probiotic casei DN-114001 showed that the incidence of winter infections was not different than in the placebo group, but the duration of all pathologies was significantly lower in the intervention group (7.0-3.2 d) when compared to the control group (8.7-3.7 d)[30].

One double-blind study, which involved 24 elderly patients who had undergone artificial enteral nutrition, evaluated the effects of a 12-wk administration of fermented milk containing *Lactobacillus johnsonii* LA1. The group who took the probiotic had significantly fewer days with infections at the end of the intervention: a decrease from 15.4% of days with infection to 5.7% was observed, and this reduction was significantly greater than that recorded for the control group[31].

Numerous studies conducted in the elderly population have shown that the intake of probiotics determines a reduced frequency and/or duration of episodes of antibiotic-associated diarrhea (AAD), in addition to reducing the severity of symptoms. Probiotics have been used in combination with antibiotics as therapy for *Clostridium difficile*, which represents 20% to 25% of cases of AAD, causing more than 95% of cases of pseudomembranous colitis[32]. A study of Hickson *et al*[33] evaluated 135 hospitalized patients, with an average age of 74 years, before and after 1 wk of consumption of 100 g (97 mL) of a drink containing *Lactobacillus casei*, *L bulgaricus* and *Streptococcus thermophilus* taken twice per day during a course of antibiotics. The placebo group received a sterile milkshake. As a primary outcome the appearance of antibiotic-associated diarrhea was considered, while a secondary outcome, the presence of *Clostridium difficile* toxin and diarrhea were identified. The results showed that 7/57 (12%) of those taking the probiotic drink developed diarrhea associated with

Table 1 Changes in the composition of the microbiota of the treated group when compared to the placebo group

Design of the study	Subjects	Age	Probiotics	Results in intervention *vs* placebo	Ref.
Double blinded controlled trial	*n* = 33 placebo group;	83 ± 7 yr	Oat drink fermented with Bifidobacter um longum and *B. longum*	↑*B.catenulatum* ↑*B. bifidum* ↑*B. breve*	Lahtinen *et al*[28]
	n = 33 control group	84 ± 8 yr			
Double blinded controlled trial	*n* = 20 placebo; *n* = 20 low dose of probiotics; *n* = 20 medium dose of probiotics; *n* = 20 high dose of probiotics	> 60 yr	Reconstituted skim milk containing *Bifidobacterium lactis*	↑*Bifidobatteri* ↑*Lactobacilli* ↑*Enterococci* ↓*Enterobatteri*	Ahmed *et al*[29]
Double blinded controlled trial	*n* = 9 placebo	Mean 71 yr	*Bifidobacterium bifidum* and *B. lactis*	↑*Bifidobacteria*	Bartosch *et al*[4]
	n = 9 symbionts (mixture of probiotics and prebiotics)	Mean 73 yr	together with inulin	↑*Lactobacilli* ↓*B. bifidum*	

antibiotic use, compared with 19/56 (34%) of the placebo group (P = 0.007). Logistic regression for control of other factors gave an odds ratio of 0.25 (95%CI: 0.07-0.85) for the use of probiotics. The absolute risk reduction was 21.6% (6.6%-36.6%). No one in the group that received the probiotic and 9/53 (17%) in the placebo group had diarrhea due to *Clostridium difficile* (P = 0.001). The absolute risk reduction was 17% (7%-27%).

A further study on the use of probiotics as adjuvants to antibiotic therapy for the preventing of gastrointestinal disorders was conducted by Beausoleil in 89 elderly men with a mean age of 72 years[34]. The preparation employed was a fermented milk containing at least 50 × 10^9 colony-forming units of *L acidophilus* CL1285 and *L casei*. The scheme of administration was 49 g once a day for two days, followed by 98 g once a day to cover the entire duration of antibiotic treatment. The antibiotic-associated diarrhea occurred in 7 out of 44 patients (15.9%) in the group that received *lactobacilli* and in 16 out of 45 patients (35.6%) in the placebo group (OR = 0.34, 95%CI: 0.125-0.944, P = 0.05). The median length of hospital stay was eight days in the group that received the probiotics, compared to 10 d in the placebo group (P = 0.09). The prevention of CDAD is an important result to be considered in the elderly population, because this condition has been associated with increased mortality and morbidity[35].

In the elderly, constipation is a common condition characterized by a constellation of symptoms defined by the criteria "Rome Ⅲ criteria"[36]. A review published in 2010[37], included 3 double-blind, placebo-controlled studies conducted by Koebnick *et al*[38], Möllenbrink *et al*[39], and by Yang *et al*[40]: as a whole 266 patients were evaluated and the most of them were elderly patients. This review confirmed the efficacy of treatment with *Bifidobacterium lactis* DN-173010, *Lactobacillus casei Shirota*, and *E. coli Nissle* 1917 on the frequency of defecation and stool consistency. This improvement is secondary to the decrease of the colonic pH value that follows the probiotics intake, thanks to the production of short chain fatty acids (butyric acid, propionic acid and lactic acid). A lower pH enhances peristalsis in the colon, and thereafter, it may decrease the intestinal transit time[37].

A double blind *vs* placebo study conducted by Ouwehand *et al*[41] studied the effects of a symbiotic combination of lactitol and *Lactobacillus acidophilus* NCFM (total daily dose of 10 g lactitol and 2 × 10^{10} cells probiotic bacteria) taken twice a day for 2 wk, in a group of elderly subjects. The results of the study showed a higher frequency of evacuation in the group that received the probiotic, as well as significantly higher levels of PGE2, as well as a changes of IgA level and spermidine, thus demonstrating positive effects on the function of the intestinal mucosa.

The same working group[42] recently assessed by means of a double- blind, placebo-controlled trial, the efficacy of the same combination of *Lactobacillus acidophilus* NCFM and lactitol in 51 elderly people who followed NSAIDs treatment. Before, during and after the intervention period, the amount of six stool bacterial phylogenetic groups was determined using quantitative PCR, and variations in the composition of total microbiota were assessed by percent profiling guanine-plus-cytosine. The results of the study showed an increase of lactobacilli and bifidobacteria and also a possible stabilizing effect on the levels of *B. coccoides-E.* XIVab and *Clostridium cluster*.

CONCLUSION

The changes in the microbiota associated with aging are still far from being clarified with certainty, but there are numerous studies that suggest that aging has a significant effect on the microbiota.

Alterations in the intestinal microbiota of the elderly may not necessarily be caused by aging, but they can be consequent to conditions that occur frequently in the elderly, such as the decline of the general state of health or malnutrition or increased need for medication (*i.e.*, antibiotics and nonsteroidal anti-inflammatory drugs). Differences in the composition of the microbiota have been

found when healthy elderly and hospitalized or institutionalized elderly subjects were compared. This further indicates that the living conditions, health status, nutrition and drugs have a significant effect on the composition of the microbiota.

When compared to young adult populations, elderly subjects show a reduction in the diversity of the microbiota, which is usually characterized by a large interindividual variability, with a lower number of *Firmicutes*, *Bifidobacteria*, *Clostridium cluster* XIV, *Faecalibacterium Prausnitzii*, *Blautia coccoides-Eubacterium rectal* and a higher number of *Enterobacteriaceae* and *Bacteroidetes.* In the elderly, the intake of and NSAIDs is followed by a significant change on the composition of the microbiota. A reduction in the proportion of the known butyrate producers belonging to *Clostridium cluster* XIV, as *Roseburia* and *Ruminococcus*, and, in the *Actinobacteria* group, a lower number of *Collinsella* spp. has been reported in elderly subjects taking NSAIDs when compared to both young adults and elderly subjects who are not taking NSAIDs.

The use of probiotics in elderly population is safe and could represent an interesting support to prevent or treat AAD, in addition to reducing the severity of symptoms, other than to help the management of constipation.

REFERENCES

1 **Egger M,** Smith GD, Altman DG, editors. Systematic reviews in health care: meta-analysis in context. 2nd ed. London, England: BMJ Books, 2001: 248-282 [DOI: 10.1002/9780470693926]

2 **Dethlefsen L**, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol* 2008; **6**: e280 [PMID: 19018661 DOI: 10.1371/journal.pbio.0060280]

3 **Mäkivuokko H**, Tiihonen K, Tynkkynen S, Paulin L, Rautonen N. The effect of age and non-steroidal anti-inflammatory drugs on human intestinal microbiota composition. *Br J Nutr* 2010; **103**: 227-234 [PMID: 19703328 DOI: 10.1017/S0007114509991553]

4 **Bartosch S**, Fite A, Macfarlane GT, McMurdo ME. Characterization of bacterial communities in feces from healthy elderly volunteers and hospitalized elderly patients by using real-time PCR and effects of antibiotic treatment on the fecal microbiota. *Appl Environ Microbiol* 2004; **70**: 3575-3581 [PMID: 15184159 DOI: 10.1128/AEM.70.6.3575-3581.2004]

5 **Hopkins MJ**, Sharp R, Macfarlane GT. Age and disease related changes in intestinal bacterial populations assessed by cell culture, 16S rRNA abundance, and community cellular fatty acid profiles. *Gut* 2001; **48**: 198-205 [PMID: 11156640 DOI: 10.1136/gut.48.2.198]

6 **Stephen AM**, Wiggins HS, Cummings JH. Effect of changing transit time on colonic microbial metabolism in man. *Gut* 1987; **28**: 601-609 [PMID: 3596341 DOI: 10.1136/gut.28.5.601]

7 **Pontes FA**, Silva AT, Cruz AC. Colonic transit times and the effect of lactulose or lactitol in hospitalized patients. *Eur J Gastroenterol Hepatol* 1995; **7**: 441-446 [PMID: 7614107]

8 **Bazzocchi G**, Ellis J, Villanueva-Meyer J, Jing J, Reddy SN, Mena I, Snape WJ. Postprandial colonic transit and motor activity in chronic constipation. *Gastroenterology* 1990; **98**: 686-693 [PMID: 2404826]

9 **Ross DG**. Subjective data related to altered bowel elimination patterns among hospitalized elder and middle-aged persons. *Orthop Nurs* 1993; **12**: 25-32 [PMID: 8233576 DOI: 10.1097/00006416-199309000-00007]

10 **Lovat LB**. Age related changes in gut physiology and nutritional status. *Gut* 1996; **38**: 306-309 [PMID: 8675079 DOI: 10.1136/gut.38.3.306]

11 **Smith JL**. Foodborne illness in the elderly. *J Food Prot* 1998; **61**: 1229-1239 [PMID: 9766083]

12 **Percival RS**, Marsh PD, Challacombe SJ. Serum antibodies to commensal oral and gut bacteria vary with age. *FEMS Immunol Med Microbiol* 1996; **15**: 35-42 [PMID: 8871114 DOI: 10.1111/j.1574-695X.1996.tb00356.x]

13 **O'Toole PW,** Claesson MJ. Gut microbiota: changes throughout the lifespan from infancy to elderly. *Int Dairy J* 2010; **20:** 281-291 [DOI: 10.1016/j.idairyj.2009.11.010]

14 **Claesson MJ**, Cusack S, O'Sullivan O, Greene-Diniz R, de Weerd H, Flannery E, Marchesi JR, Falush D, Dinan T, Fitzgerald G, Stanton C, van Sinderen D, O'Connor M, Harnedy N, O'Connor K, Henry C, O'Mahony D, Fitzgerald AP, Shanahan F, Twomey C, Hill C, Ross RP, O'Toole PW. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. *Proc Natl Acad Sci USA* 2011; **108** Suppl 1: 4586-4591 [PMID: 20571116 DOI: 10.1073/pnas.1000097107]

15 **Biagi E**, Nylund L, Candela M, Ostan R, Bucci L, Pini E, Nikkïla J, Monti D, Satokari R, Franceschi C, Brigidi P, De Vos W. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. *PLoS One* 2010; **5**: e10667 [PMID: 20498852 DOI: 10.1371/journal.pone.0010667]

16 **Woodmansey EJ**. Intestinal bacteria and ageing. *J Appl Microbiol* 2007; **102**: 1178-1186 [PMID: 17448153 DOI: 10.1111/j.1365-2672.2007.03400.x]

17 **Mueller S**, Saunier K, Hanisch C, Norin E, Alm L, Midtvedt T, Cresci A, Silvi S, Orpianesi C, Verdenelli MC, Clavel T, Koebnick C, Zunft HJ, Doré J, Blaut M. Differences in fecal microbiota in different European study populations in relation to age, gender, and country: a cross-sectional study. *Appl Environ Microbiol* 2006; **72**: 1027-1033 [PMID: 16461645 DOI: 10.1128/AEM.72.2.1027-1033.2006]

18 **Rajilić-Stojanović M**, Heilig HG, Molenaar D, Kajander K, Surakka A, Smidt H, de Vos WM. Development and application of the human intestinal tract chip, a phylogenetic microarray: analysis of universally conserved phylotypes in the abundant microbiota of young and elderly adults. *Environ Microbiol* 2009; **11**: 1736-1751 [PMID: 19508560 DOI: 10.1111/j.1462-2920.2009.01900.x]

19 **He T,** Harmsen H, Raangs G, Welling GW. Composition of faecal microbiota of elderly people. *Microb Ecol Health* 2003; **15:** 153-159 [DOI: 10.1080/08910600310020505]

20 **Blaut M,** Marteau P, Miller GD. Probiotics and the intestinal microflora. What impact on the immune system, infections and ageing? *Curr Nutr Food Sci* 2006; **2:** 79-95 [DOI: 10.2174/157340106775472029]

21 **Claesson MJ**, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, Harris HM, Coakley M, Lakshminarayanan B, O'Sullivan O, Fitzgerald GF, Deane J, O'Connor M, Harnedy N, O'Connor K, O'Mahony D, van Sinderen D, Wallace M, Brennan L, Stanton C, Marchesi JR, Fitzgerald AP, Shanahan F, Hill C, Ross RP, O'Toole PW. Gut microbiota composition correlates with diet and health in the elderly. *Nature* 2012; **488**: 178-184 [PMID: 22797518 DOI: 10.1038/nature11319]

22 **van Tongeren SP**, Slaets JP, Harmsen HJ, Welling GW. Fecal microbiota composition and frailty. *Appl Environ Microbiol* 2005; **71**: 6438-6442 [PMID: 16204576 DOI: 10.1128/AEM.71.10.6438-6442.2005]

23 **Guigoz Y**, Doré J, Schiffrin EJ. The inflammatory status of old age can be nurtured from the intestinal environment. *Curr Opin Clin Nutr Metab Care* 2008; **11**: 13-20 [PMID: 18090652 DOI: 10.1097/MCO.0b013e3282f2bfdf]

24 **Faith JJ**, McNulty NP, Rey FE, Gordon JI. Predicting a human gut microbiota's response to diet in gnotobiotic mice. *Science* 2011; **333**: 101-104 [PMID: 21596954 DOI: 10.1126/science.1206025]

25 **Wu GD**, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh

SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman FD, Lewis JD. Linking long-term dietary patterns with gut microbial enterotypes. *Science* 2011; **334**: 105-108 [PMID: 21885731 DOI: 10.1126/science.1208344]

26 **Walker AW**, Ince J, Duncan SH, Webster LM, Holtrop G, Ze X, Brown D, Stares MD, Scott P, Bergerat A, Louis P, McIntosh F, Johnstone AM, Lobley GE, Parkhill J, Flint HJ. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *ISME J* 2011; **5**: 220-230 [PMID: 20686513 DOI: 10.1038/ismej.2010.118]

27 **Hartikainen S**, Mäntyselkä P, Louhivuori-Laako K, Enlund H, Sulkava R. Concomitant use of analgesics and psychotropics in home-dwelling elderly people-Kuopio 75 + study. *Br J Clin Pharmacol* 2005; **60**: 306-310 [PMID: 16120070 DOI: 10.1111/j.1365-2125.2005.02417.x]

28 **Lahtinen SJ**, Tammela L, Korpela J, Parhiala R, Ahokoski H, Mykkänen H, Salminen SJ. Probiotics modulate the Bifidobacterium microbiota of elderly nursing home residents. *Age* (Dordr) 2009; **31**: 59-66 [PMID: 19234769 DOI: 10.1007/s11357-008-9081-0]

29 **Ahmed M**, Prasad J, Gill H, Stevenson L, Gopal P. Impact of consumption of different levels of Bifidobacterium lactis HN019 on the intestinal microflora of elderly human subjects. *J Nutr Health Aging* 2007; **11**: 26-31 [PMID: 17315077]

30 **Turchet P**, Laurenzano M, Auboiron S, Antoine JM. Effect of fermented milk containing the probiotic Lactobacillus casei DN-114001 on winter infections in free-living elderly subjects: a randomised, controlled pilot study. *J Nutr Health Aging* 2003; **7**: 75-77 [PMID: 12679825]

31 **Fukushima Y**, Miyaguchi S, Yamano T, Kaburagi T, Iino H, Ushida K, Sato K. Improvement of nutritional status and incidence of infection in hospitalised, enterally fed elderly by feeding of fermented milk containing probiotic Lactobacillus johnsonii La1 (NCC533). *Br J Nutr* 2007; **98**: 969-977 [PMID: 17617944 DOI: 10.1017/S0007114507764723]

32 **Gougoulias C,** Tuohy KM, Gibson GR. Dietary based gut flora modulation against Clostridium difficile onset. *Food Sci Tech Bull Funct Foods* 2007; **4:** 31-41 [DOI: 10.1616/1476-2137.14986]

33 **Hickson M**, D'Souza AL, Muthu N, Rogers TR, Want S, Rajkumar C, Bulpitt CJ. Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. *BMJ* 2007; **335**: 80 [PMID: 17604300 DOI: 10.1136/bmj.39231.599815.55]

34 **Beausoleil M**, Fortier N, Guénette S, L'ecuyer A, Savoie M, Franco M, Lachaine J, Weiss K. Effect of a fermented milk combining Lactobacillus acidophilus Cl1285 and Lactobacillus casei in the prevention of antibiotic-associated diarrhea: a randomized, double-blind, placebo-controlled trial. *Can J Gastroenterol* 2007; **21**: 732-736 [PMID: 18026577]

35 **Miller MA**, Hyland M, Ofner-Agostini M, Gourdeau M, Ishak M. Morbidity, mortality, and healthcare burden of nosocomial Clostridium difficile-associated diarrhea in Canadian hospitals. *Infect Control Hosp Epidemiol* 2002; **23**: 137-140 [PMID: 11918118 DOI: 10.1086/502023]

36 **Higgins PD**, Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol* 2004; **99**: 750-759 [PMID: 15089911 DOI: 10.1111/j.1572-0241.2004.04114.x]

37 **Chmielewska A**, Szajewska H. Systematic review of randomised controlled trials: probiotics for functional constipation. *World J Gastroenterol* 2010; **16**: 69-75 [PMID: 20039451 DOI: 10.3748/wjg.v16.i1.69]

38 **Koebnick C**, Wagner I, Leitzmann P, Stern U, Zunft HJ. Probiotic beverage containing Lactobacillus casei Shirota improves gastrointestinal symptoms in patients with chronic constipation. *Can J Gastroenterol* 2003; **17**: 655-659 [PMID: 14631461]

39 **Möllenbrink M**, Bruckschen E. [Treatment of chronic constipation with physiologic Escherichia coli bacteria. Results of a clinical study of the effectiveness and tolerance of microbiological therapy with the E. coli Nissle 1917 strain (Mutaflor)]. *Med Klin* (Munich) 1994; **89**: 587-593 [PMID: 7815986]

40 **Yang YX**, He M, Hu G, Wei J, Pages P, Yang XH, Bourdu-Naturel S. Effect of a fermented milk containing Bifidobacterium lactis DN-173010 on Chinese constipated women. *World J Gastroenterol* 2008; **14**: 6237-6243 [PMID: 18985817 DOI: 10.3748/wjg.14.6237]

41 **Ouwehand AC**, Tiihonen K, Saarinen M, Putaala H, Rautonen N. Influence of a combination of Lactobacillus acidophilus NCFM and lactitol on healthy elderly: intestinal and immune parameters. *Br J Nutr* 2009; **101**: 367-375 [PMID: 18634707 DOI: 10.1017/S0007114508003097]

42 **Björklund M**, Ouwehand AC, Forssten SD, Nikkilä J, Tiihonen K, Rautonen N, Lahtinen SJ. Gut microbiota of healthy elderly NSAID users is selectively modified with the administration of Lactobacillus acidophilus NCFM and lactitol. *Age* (Dordr) 2012; **34**: 987-999 [PMID: 21853265 DOI: 10.1007/s11357-011-9294-5]

P- Reviewer: Dore MP, Lee HC, Marotta F **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Lu YJ

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: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com