International Journal of Medical Microbiology 308 (2018) 487–497

Contents lists available at ScienceDirect

International Journal of Medical Microbiology

journal homepage: www.elsevier.com/locate/ijmm

Human microbiome restoration and safety

Eric Banan-Mwine Daliri[a], Charles Nkufi Tango[a], Byong H. Lee[b], Deog-Hwan Oh[a,*]

[a] Department of Food Science and Biotechnology, Kangwon National University, Chuncheon, 24341, South Korea
[b] Department of Microbiology/Immunology, McGill University, Montreal, QC, H3A 2B4, Canada

ARTICLE INFO

Keywords:
Dysbiosis
Fecal microbiota transplant
Metagenomics
Antibiotic resistance

ABSTRACT

The human gut microbiome consists of many bacteria which are in symbiotic relationship with human beings. The gut microbial metabolism, as well as the microbial-host co-metabolism, has been found to greatly influence health and disease. Factors such as diet, antibiotic use and lifestyle have been associated with alterations in the gut microbial community and may result in several pathological conditions. For this reason, several strategies including fecal microbiota transplant and probiotic administration have been applied and proven to be feasible and effective in restoring the gut microbiota in humans. Yet, safety concerns such as potential health risks that may arise from such interventions and how these strategies are regulated need to be addressed. Also, it will be important to know if these microbiome restoration strategies can have a profound impact on health. This review provides an overview of our current knowledge of the microbiome restoration strategies and safety issues on how these strategies are regulated.

1. Introduction

The gut microbial ecosystem consists of large numbers of bacteria, archaea, fungi, viruses and yeasts making humans superorganisms (Lloyd-Price et al., 2016). From the mouth to the anus, this ostensible organ (the microbiome) performs several metabolic functions that influence host physiology in diverse ways (Musso et al., 2011; Raj et al., 2012). In fact, although important vitamins such as folate, thiamine, biotin, panthothenic acid, riboflavin and vitamin K are available in diet, the gut bacteria also synthesize these vitamins in the host (Hill, 1997). However, an individual's life style, diet and immune system may affect the composition and functions of the gut microbiota (Ishimwe et al., 2015) and increase the risk of diseases such as myalgic encephalomyelitis/chronic fatigue syndrome (Giloteaux et al., 2016), obesity, *Clostridioides difficile* (formally *Clostridium difficile*) infection (CDI), ulcerative colitis (UC), irritable bowel syndrome (IBS) and diabetes (Wang et al., 2017). Recent advances in gene sequencing technologies have made it possible to easily characterize the microbiome and study the changes that occur under various conditions. For instance, it is reported that UC patients generally have lower levels of Firmicutes (*Clostridium* clusters XIVa and IV) and Bacteroidetes with significant abundance of *Peptostreptococcus sp.*, *Fusobacterium* sp., *Campylobacter* sp. and *Helicobacter sp* which are opportunistic pathogens (Rajilic-Stojanovic et al., 2013). Also, recent findings have shown that the levels of short chain fatty acid producers such as *Faecalibacterium prausnitzii* and *Roseburia* spp are significantly reduced while the levels of opportunistic pathogens such as *Streptococcus* spp., *Klebsiella* spp., and *Parabacteroides merdae* increase during hypertension (Yan et al., 2017). Although it is possible that the changes observed in the gut bacteria communities of a patient may be caused by the disease, studies have shown that activities that result in loss of gut microbial richness (e.g, overuse of antibiotics) also result in pathological conditions (Abt et al., 2016). This suggests that a modification of the gut microbiota to restore its diversity may be helpful in treating diseases associated with dysbiosis. The most studied factors that alter the microbiome are diet and antibiotics. A few studies have also shown the impacts of lifestyle on the gut microbiota.

1.1. Diet and the gut microbiota

Diet does not only provide nutrients to the body, but also influences health by modulating the composition and diversity of the gut microbiota (Guaraldi and Salvatori, 2012; Rothe and Blaut, 2012). A comparison of the gut microbiome of unindustrialized rural communities in Malawi, Tanzania, Venezuela and Papua New Guinea with that of industrialized communities in Italy and USA has revealed specific gut

Abbreviations: FMT, fecal microbiota transplant; CDI, *Clostridioides difficile* infection; CDAD, *Clostridioides difficile associated diarrhea*; CD, Crohn's disease; UC, ulcerative colitis; IBS, irritable bowel syndrome; IBD, inflammatory bowel disease; EU, European Union; BF, Burkina Faso; FDA, Food and Drug Administration; IND, investigational new drug; CTA, clinical trial application; NAPE, *N*-acyl phosphatidyl ethanolamine; FAO, Food and Agriculture Organization; WHO, World Health Organization

* Corresponding author.
E-mail address: deoghwa@kangwon.ac.kr (D.-H. Oh).

https://doi.org/10.1016/j.ijmm.2018.05.002
Received 22 November 2017; Received in revised form 4 April 2018; Accepted 7 May 2018

microbial adaptations to their respective diets and lifestyle (Martínez et al., 2015; Segata, 2015). The gut of the unindustrialized rural communities (such as hunter-gatherers and rural agriculturalist communities) were found to be enriched with microbial communities such as Prevotella and *Treponema* sp, which enhance the degradation of the high fiber diet whereas westernization (consumption of Western diet: low fibre, high sugar, high fat and high animal protein) consistently increased the proportions of Bacteroides, Ruminococcus, Faecalibacterium, Alistipes, Bilophila and Blautia (Obregon-Tito et al., 2015; Schnorr et al., 2014; Wu et al., 2011; Yatsunenko et al., 2012).

Recent studies have shown that certain microbial taxa in the microbiome could seasonally disappear and reappear due to seasonal food availability (Davenport et al., 2014; Dubois et al., 2017; Smits et al., 2017). These observations prove the plastic nature of the gut microbiome as a result of dietary changes. Other studies have demonstrated that animal-based diets could increase the abundance of bile-tolerant microorganisms such as Alistipes, Bilophila and Bacteroides while decreasing the levels of Firmicutes (Roseburia, *Eubacterium rectale* and *Ruminococcus bromii*) in the gut (David et al., 2014). De Filippo et al. (2010) compared the impact of western diet (high in animal protein and fat) and rural African diet (high in fiber, low in animal protein) on the fecal microbiota of European children (EU) and children in Burkina Faso (BF). 16S rRNA analysis showed high levels of Bacteroidetes and depletion in Firmicutes in the fecal matter of the children from BF while EU children had high numbers of Enterobacteriaceae. BF children also had high levels of bacteria from the genera Prevotella and Xylanibacter which hydrolyze cellulose and xylose respectively. Such bacteria were however absent in EU children. They concluded that the microbiota of the people in Burkina Faso may have co-evolved with the polysaccharide-rich diet to enable maximum energy intake from dietary fibers. A controlled-feeding study by Wu et al. (2011) also reported the possibility of the microbiome composition to change significantly within 24 h of initiating a high-fat/low-fiber or low-fat/high-fiber diet and that, long-term diet could cause a shift in the abundance in the core microbial communities. A report from Matijašić et al. (2014) is consistent with this claim as they also observed that long-term vegetarian diet patterns could result in an increase in fiber digesting bacteria such as *Bacteroides thetaiotaomicron*, *Clostridium clostridioforme* and *Faecalibacterium prausnitzii* while the relative abundance of Clostridium cluster XIVa could decrease in the gut. Omnivores have been reported to have higher populations of *Bifidobacterium, Streptococus, Collinsella* and Lachnospiraceae and lower populations of *Subdoligranulum*.

1.2. Antibiotics and the gut microbiota

Antibiotic use has been a common method for treating diseases caused by bacteria infection (Cammarota et al., 2015). However, many concerns have risen from the use of antibiotics in treating pathogenic infections since they may alter the diversity and functional capacity of the dominant gut microbiome (Dubourg et al., 2013; Jakobsson et al., 2010) and such alterations could result in different physiological states. For instance, administration of fluoroquinolones and β-lactams for seven days was reported to significantly decrease microbial diversity by 25% and core phylogenetic microbiota by 58.6% (Panda et al., 2014). Administration of a combination of ampicillin and gentamicin to infants for 4 weeks was also associated with a significant increase in the levels of Proteobacteria and low Actinobacteria populations in their feces relative to the untreated infants (Fouhy et al., 2012). Animal studies have shown that, even low doses of antibiotics may perturb the microbiota during maturation and reduce immune response. This can eventually affect host metabolism significantly and increase the risk of obesity (Cho et al., 2012; Cox et al., 2014). A similar observation was reported in human studies where babies exposed to antibiotics at very early stages in life (< 6 months) increased in body mass from 10 to 38 months making them susceptible to obesity (Trasande et al., 2013). Also, an examination of 979 children during their first 10 years of life showed that repeated exposure to antibiotics (especially β-lactam agents) in early life could result in increased body weight (Mbakwa et al., 2016). Similarly, a population-based cohort study involving 21,714 children in the United Kingdom reported that children who were exposed to antibiotics before age 2 years had higher risks of becoming obese at age 4 years (Scott et al., 2016). Although it may be difficult to attribute obesity epidemics to antibiotic administration (as a main factor) and the fact that other studies found no association between antibiotic exposure and infant obesity (Gerber et al., 2016), the adverse effects on the microbiota cannot be ignored. Yet, current studies have only reported associations between antibiotic consumption and changes in the gut microbiome but have not demonstrated causality. Well-designed studies that prove that antibiotic consumption alters gut microbial richness and results in specific disease phenotypes will be helpful in understanding the reported observations.

Indeed, administration of antibiotics can cause antibiotic resistant bacteria such as vancomycin resistant Enterococcus faecium to grow well in the gut when colonization resistance against pathogenic bacteria is compromised (Abt et al., 2016). Such bacteria may capitalize on the compromised colonization resistance to grow to extremely high levels that can lead to bloodstream invasion and sepsis. *Clostridioides difficile*-associated diarrhea (CDAD) is another typical example of how antibiotics may perturb the microbiota and affect a patient's health. Treatment of CDAD with vancomycin or metronidazole has been associated with depletion of the microbiota and recurrence of symptoms occur in about 10–20% of patients after initial therapy and about 40-65% in patients who are treated for a second episode (Abdelfatah et al., 2015; Bauer et al., 2011). After the first recurrence, either vancomycin

Table 1
Recommended Treatment Options for the First Episode of CDI.

Recommended Therapy	Dose	Remarks
Vancomycin	Mild to severe cases: 125 mg 4 × daily for 10-14 days. Severe complicated cases: 250-500 mg (oral) 4 × daily.	• Increases the risk of VRE (Abt et al., 2016) • Superior to metronidazole for treating moderate to severe CDI (Stevens et al., 2017).
Zinplava (bezlotoxumab)	Recurrent CDI: 10 mg/kg intravenously infused over 1 hr as a single dose	• Heart failure among people with a history of congestive heart failure (Markham, 2016).
Metronidazole	Mild CDI: 500 mg 3 times daily for 10 days (oral and intravenous)	• Less effective compared to other options for treating CDI (Markham, 2016).
Rifaximin	All forms of CDI: 400-550 mg 2 × daily for 14 days	• Not approved by USFDA for treatment
Tigecycline	Refractory CDI cases: 100 mg (intravenous), then 50 mg IV twice daily	• Not approved for treatment • Can be used as rescue treatment for patients with severe CDI when treatment with vancomycin and metronidazole fails (Britt et al., 2014).
Fidaxomicin	All forms of CDI: 200 mg (oral) 2 × daily for 10 days	• Preserves the gut microflora (Louie et al., 2012). • Less likely to promote VRE (Nerandzic et al., 2012). • Relatively more expensive than other antibiotic treatments (Al-Jashaami and DuPont, 2016).
Nitazoxanide	All forms of CDI: 500 mg (oral) twice daily for 10 days	• Not approved for treatment