Mini-Review

The gastrointestinal microbiome and the enteropathogenetic syndromes: an infectious diseases perspective

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Abstract: Increasing body of evidence suggests that human microbiota has an essential role in human health. The dynamic interactions between humans and their microbiota are most clearly demonstrated in the gastrointestinal tract because of the higher density. So far, we understand very little about these complex interactions, but data regarding the use of fecal microbiota transplantation (FMT) in *C. difficile* infections (CDI) suggest that restoring microbiome is clinically effective. Nowadays, the gastrointestinal tract is well recognized as the main "reservoir" not only for *C. difficile* but also for *Candida* spp. infections and for multidrug resistant bacteria such as carbapenemase-producing *K. pneumoniae* (CP-Kp). In order to stress the importance of gastrointestinal alterations in promoting intestinal colonization, overgrowth and diseases by these pathogens, we proposed the term "enteropathogenetic syndromes", to describe enteropathogenetic endogenous opportunistic infections caused by *Candida* spp, *C. difficile* and CP-Kp. To reduce the opportunity of enteropathogenetic syndromes, there is a strong need for new antimicrobial stewardship approaches, aiming to reduce antimicrobial consumption, thus protecting and maintaining the gut microbiota. Aim of this review is to discuss the importance of gut micobiota alterations in the development of enteropathogenetic syndromes by an infectious diseases perspective.

Keywords: Gastrointestinal microbiome; *C. difficile*; *Candida*; CP-Kp; multidrug resistant bacteria; colonization; CRE; fecal transplant

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Introduction

Human microbiota refers to all of the microbes that are present in a specific "habitat", for example the skin or mouth, intestinal tract or vagina and in recent years, increasing evidences demonstrated that human microbiota plays a crucial role in maintaining human health (1,2). Traditional cultured based methods capture only small proportion of all bacterial microbiota, but next generation sequencing DNA has closed this gap (3-5). Several data from US (HMP) or European Microbiome Project (MetaHIT) have shown, through 16S rRna analysis, that a subset of microbial genes can be found in the majority of healthy individuals, known as "core microbiome", whereas there are variable components that may be typical of specific ethnic group, or that can be associated with geographic locations, dietary habits and diseases (3-9).

The stable healthy microbial community, which is known as colonization resistance, consistently provides protection against enteric pathogens, nutrients from food, and immune system regulation (3,4). The dynamic interactions between host and its microbiota are most clearly demonstrated in the gastrointestinal tract where the microbiota populate at a higher density. Changes in gut microbiota composition are closely related to health: this crucial defense mechanism

can be impaired by several factors such as treatment with antibiotics or chemotherapy, and patients may become carriers of pathogenic bacteria, including strains that are resistant to treatment [multidrug resistant (MDR)] (10-12). The extensive use of broad-spectrum antibiotics has been linked to the spread of antimicrobial resistance in the last ten years and antimicrobial resistance is an increasing threat to human health (12).

Intestinal acquisition of resistant bacteria over the healthy microbiota is well known to be one of the major risk factor for the development of invasive infection by MDR bacteria, such as carbapenemase-producing *K. pneumoniae* (CP-Kp) or by *Candida* (13,14). Modulation of the gut microbiota might be an effective treatment strategy for restoring healthy function; however, the precise effect of antibiotics on the intestinal microbiota and the effect on the acquisition and the overgrowth of MDR bacteria needs to be further investigated.

Aim of this review is to discuss the role of gut microbiota alterations in the pathogenesis of invasive infections by MDR resistant organism and *Candida* by an infectious diseases perspective.

Gut microbiome

Two major phyla, *Bacteroidetes* and *Firmicutes*, dominate the healthy gut microbiota (15). Approximately 1.5 kg of bacteria lives in the human intestinal tract, and anaerobes are found at 100–1,000 time that of aerobes and facultative aerobes (2). Even if this general profile remains constant, gut microbiota exhibits both temporal and spatial shift in species distribution. From the esophagus distally to the rectum, there is a marked difference in diversity and number of bacteria ranging from 10 per gram of contents in the esophagus and stomach to 10^{12}/gram of contents in the colon and distal gut. The large intestine constitutes over 70% of all microbes and they are generally identified by stool samples (16).

Microbiota begins to inhabit the human intestinal tract after vaginal birth, with facoltative aerobes as earliest resident, such as *E. coli*, *Streptococci* or *Enterococcus* spp. Normal gut microbiota has several functional aspects, such as defense against pathogens, cell proliferation and differentiation, mucus secretion, and barrier function; furthermore it has anti-inflammatory and antioxidative effects and it acts as antimicrobial protection by protecting mucosal barrier function (15). In fact, the integrity of the gut barrier is maintained by modulation of expression of proteins required for maintenance of desmosomes at epithelial villus as well as stimulation of microbial cell wall peptidoglycan or transcription of angiogenin factor 3, implicated in the development of intestinal microvasculature. The other mechanism to supervise the overgrowth of pathogenic strains is by inducing local immunoglobulins A through activation of intestinal dendritic cells (17).

During prolonged antibiotic treatments, gut microbiota can be affected by collateral damage, becoming a significant "reservoir" of MDR microorganisms with a "nosocomial profile" of antibiotic resistance. In fact, MDR bacteria that are not eliminated by antibiotic treatment, can proliferate and reach higher density in the intestinal lumen (11). In *C. difficile* infections (CDI) the causal role of a dysbiotic microbiota is well known, and it has been suggested that similar alterations may favor intestinal colonization by CP - Kp (18).

Intestinal colonization by CP-Kp seems to be one of the most important risk factors for the development of CP-Kp invasive infections and selective digestive tract decontamination (SDD) of colonized patients with non-absorbed antibiotics has been suggested to reduce transmission and prevent invasive infections, although concerns are rising regarding the risk of resistance in patients who fail to respond to gut decontamination (13,19-21).

In clinical practice, colonized patients pose an epidemiological threat to other hospitalized individuals but are also in danger of developing systemic infections with gut-colonizing microorganisms, with a higher risk in the hematological setting (22).

Evidence for GI microbiome modifications

The composition of human microbiota is easily regulated by many environmental factors, particularly age, diet and antibiotic use (23). The effects of diet are well described from first year of life, since breast-fed infants are colonized by Bifidobacteria whilst bottle fed infants harbor different bacteria such as *Bacteroides*, *Clostridium* and Enterobacteriaceae (24). Diet seems to be the most important determinant in shaping the gut microbiota for the entire human life and diet habits can affect the composition of gut microbiome, causing disbiosis or in some cases protection from diseases by increasing the proportion of specific bacteria species (25). There is some evidence that gut could be colonized by organisms *in utero*, although the first microbiota profile is now clear that is

largely shaped at delivery (26). From the age of 3, infant gut microbiota can be considered as adult microbiota since it has from 40% to 60% of similarity. Studies have shown that young children still have significant differences in proportion of *Bacteroides* and *Bifidobacterium* compared to adults. In preterm infants, there is a predominance of *Bifidobacterium* and *Lactobacillus* that can be modified, according to the type of feeding habits (27). Although the initially developing microbiota is largely influenced by feeding, several factors during life modify gut microbiota. Gut microbiota changes according to age and its composition in the elderly differs considerably between individuals, as extensively studied in the ELDERMET cohort (28-30). In this study, a shift in the microbiota toward a *Bacteroidetes*-predominated population in frailer older patients compared to younger individuals was observed (28). This large variance is probably due to external factors influencing the microbiota, such as diet, exercise and inactivity, and medication (29). Several ongoing studies, such as the NuAge project, will apply multi-omics analysis to determine if microbiota changes are related to or are the cause of health loss and how other physiological processes might influence these changes (30). This will establish any possible impact on aging health status, by or even modulating the microbiota composition and function, the possibility to target microbiota for interventions to promote healthier aging (30,31).

A strong body of evidence has now demonstrated that the use of antibiotics has long-term effects on the ecology of gut microbiota, with a reduction of taxonomic diversity and persistence of changes in the majority of individuals. Data showed that the effect of short-term use of broad-spectrum antibiotics with predominant anaerobic coverage could last up to 2 years, with a persistent depletion of the diversity of *Bacteroides* (32,33). Different studies have demonstrated that a short course of *H. pylori* eradication results in a dramatic reduction in the diversity of *Actinobacteria* that may endure over 4-year period, as well as it may lead to an overgrowth of potentially pathogenic organism including MDR Enterobacteriaceae and yeast (34,35). These data were confirmed in recent studies using molecular techniques based on analysis of 16S rRNA, in which the loss of diversity and changes in different bacteria taxa have been reported in patients treated with prolonged antibiotic therapies (36). Moreover, the antibiotic-induced alterations increase susceptibility to gastrointestinal infections, such as salmonellosis and diarrhea and colitis by *C. difficile* (37). Thus, one of the major concerns in addition to the alteration of the normal microbiota diversity, is that the use of broad spectrum antibiotics can lead to gut colonization by MDR strain of bacteria that could easily overwhelm the bloodstream (13,38).

"Enteropathogenetic Syndromes"

Dysbiosis is represented by an alteration and "imbalance" of the microbiome without any chance to physiological recovery, due to several factors. The causal role of dysbiosis is well known for CDI, in which the altered microbiome creates a favourable setting for *C. difficile* colonization, sporulation, spore germination, and toxin production. Dysbiotic state is maintained and promoted by *C. difficile* disruption of epithelial barrier function and alterations of inflammatory responses, and only an intervention targeted to restore a physiological microbiome is helpful to clear CDI (39). Thus, similar alteration may be favoring colonization of MDR bacteria such as carbapenemase producing CP-Kp or ESBL or an excessive intestinal growth of *Candida* spp, favoring bloodstream infections (40). There are some reports of candidemia following CDI, of CP-Kp bloodstream infections (BSI) associated with candidemia, of early infections by CP-Kp, and of possible interactions amongst antibiotics use to treat CDI and *Candida* colonization (40-43). Prescott *et al.* showed that in patients with previous CDI, there is a higher risk of sepsis in the 90 days after admission, related to the persistence of altered microbiota (41). Interestingly, in *in vivo* models of gastrointestinal candidiasis Cole *et al.* evaluated the role of gastrointestinal mucosa colonization, alterations of the integrity of the mucosal epithelium and damage of mucosal immunity in the development of invasive candidiasis (14).

Nowadays, it is common knowledge that the gastrointestinal tract has the crucial role of main reservoir for human diseases by *Candida* spp. and for epidemic spread of MDR bacteria such as CP-Kp and *C. difficile*. For these reasons, we proposed a new acronyme "CCC" to highlight the similar pathogenetic pathway of *Candida spp*, *C. difficile* and CP-Kp infections (38). In order to stress the importance of gastrointestinal alterations in promoting intestinal colonization, overgrowth and diseases by these pathogens, we proposed the term "enteropathogenetic syndromes", to describe enteropathogenetic endogenous opportunistic infections caused by "CCC" (18). To reduce the opportunity of enteropathogenetic syndromes, there is a strong need for new antimicrobial and antifungal stewardship approaches, aiming to reduce antimicrobial consumption, thus protecting and maintaining the gut

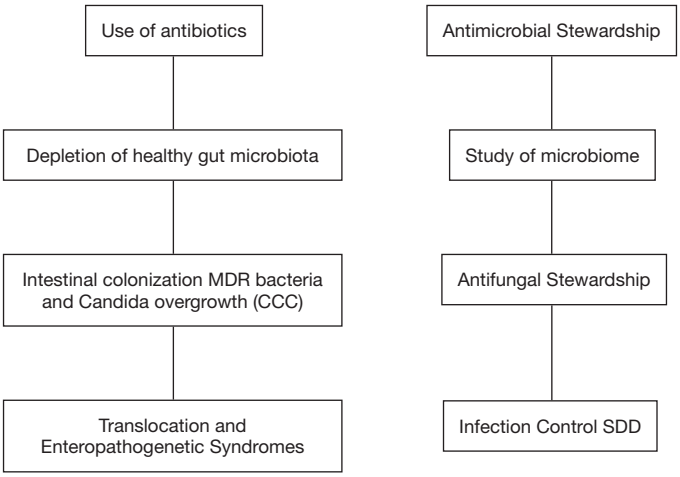

Figure 1 The gut microbioma and the enteropathogenetic syndromes (left), with possible bundle of interventions (right). MDR, multidrug resistant; CCC, *Candida*, *C. difficile*, carbapenemase; SDD, selective digestive tract decontamination.

microbiota (44) (*Figure 1*).

How to eradicate MDR colonization by CP-Kp

SDD

Along with infection control measures such as patient isolation or cohorting with dedicated staff, SDD with nonabsorbed antibiotics has been proposed as an effective strategy to reduce transmission and preventing subsequent infectious episodes in colonized patients by CP-Kp. One of the most used regimen for SDD is oral gentamicin or combination of gentamicin plus polymyxin E (45). The efficacy of SDD with gentamicin 80 mg four times daily was evaluated by Tascini *et al.* in 50 patients colonized by gentamicin-susceptible CP-Kp, with or without concomitant systemic antibiotic therapy (19). The overall decontamination rate was 68% and at the 6-month follow-up, a CP-Kp infection was observed only in 15% of successfully decontaminated patients compared to 73% of persistent carriers (19).

In our center, we proposed a multiple-step intervention strategy in hematological patients undergoing allogenic bone narrow transplantation (HSCT) colonized by CP-Kp. Steps included oral gentamicin within 20 days before HSCT, treatment of febrile neutropenia with intravenous tigecycline 100 mg bid and piperacillin-tazobactam at standard dosages and early appropriate combination therapy for patients with severe sepsis. In our small series all patients survived, no resistance to oral gentamicin was observed and 60% of patients had negative rectal swabs after transplant (21).

Lübbert *et al.* described 14 patients colonized by CP-Kp, treated with 7 days of combination of colistin and oral gentamicin, and applying colistin/gentamicin gel (0.5 g) to the oral cavity. Decolonisation of CP-Kp was achieved in 43% of patients treated with the antibiotics, but there was an increased risk of secondary resistance to colistin and gentamicin following SDD (19% and 45% increase, respectively) (46). Thus, the risk of resistance should be evaluated before starting SDD, since oral topic antibiotic therapy can be useful but may favor the emergence of resistant CP-Kp, especially in patients with failures of decontamination regimens.

Fecal microbiota transplantation (FMT)

A large body of evidence, including randomised controlled trials (RCTs), systematic reviews and meta-analyses, proved clear evidence that FMT is a highly effective treatment for CDI and based on these data both the European Society for Microbiology and Infectious Disease and the American College of Gastroenterology recommended FMT as a treatment for recurrent CDI (47-55). Promising findings suggest that FMT may play a role also in the management of other disorders associated with the alteration of gut microbiota, such as to decolonize patients from MDR bacteria. So far only case reports have been reported using FMT to decolonize from MDR bacteria, but six trials are ongoing (56-61). Regarding the safety of this procedure, no serious adverse events were reported in

any of the case reports published to date (56). However, long term monitoring of the efficacy of FMT still need to be further investigated, since current evidence suggest a temporary more than permanent decolonization from MDR bacteria (62).

Conclusions: targeting microbiota

Variability of human microbiota is closely related to health and diseases. There are many ways to regulate the composition of gut microbiota, therefore targeting the gut microbiota has been proposed as a new therapeutic approach to tackle several diseases (23). FMT for recurrent CDI is a major example of a successful approach to restore microbiota complexity, with success rates of approximately 90% (47-53). Regarding antimicrobial resistance and the battle against MDR bacteria, intestinal microbiota could be the key to prevent or eradicate MDR colonization. So far, there are no data describing which bacterial species provide the best protection against MDR colonization, thus the most promising approach might be FMT (62). So far, there are several obstacles to determine the role of microbiota in human health, first of all samples collection and methods of analysis (23). There are several methods for determining the biodiversity and 16S rRNA sequencing is the most used, although several reports have shown that different amplification strategies or sample collections were associated with different results (63,64). Shotgun whole genome sequencing is usually performed to obtain information about the composition of the microbiome and association with metabolic patterns with diseases, but standardized samples collection and analysis are important steps for successful research on microbiota. Second, microbiota is affected by dietary habits and different ethnic groups are different, highlighting another complexity for clinical studies (65). Third, integration of omics data with phenotypic data of the diseases is important. Moreover, few data are available so far, and the interaction of microbioma with human immunogenetic determinants, such as proteins and genes (66).

In conclusion, there are some basic questions that still need to be answered to understand the gut microbioma complexities and therapeutics perspectives. As we progress from an era of broad spectrum antibiotics to a more effective stewardship approaches, the knowledge of microbiome and its functions will help to individualized medicine, either preventive or curative (3,44,67). In the future targeting or restoring microbiome may represent an effective and complementary therapeutic strategy.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aoi.2017.08.02). The authors have no conflicts of interest to declare.

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