

## Eubiotic properties of rifaximin: Disruption of the traditional concepts in gut microbiota modulation

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### Abstract

Antibiotics are usually prescribed to cure infections but

they also have significant modulatory effects on the gut microbiota. Several alterations of the intestinal bacterial community have been reported during antibiotic treatment, including the reduction of beneficial bacteria as well as of microbial alpha-diversity. Although after the discontinuation of antibiotic therapies it has been observed a trend towards the restoration of the original condition, the new steady state is different from the previous one, as if antibiotics induced some kind of irreversible perturbation of the gut microbial community. The poorly absorbed antibiotic rifaximin seem to be different from the other antibiotics, because it exerts non-traditional effects additional to the bactericidal/bacteriostatic activity on the gut microbiota. Rifaximin is able to reduce bacterial virulence and translocation, has anti-inflammatory properties and has been demonstrated to positively modulate the gut microbial composition. Animal models, culture studies and metagenomic analyses have demonstrated an increase in *Bifidobacterium*, *Faecalibacterium prausnitzii* and *Lactobacillus* abundance after rifaximin treatment, probably consequent to the induction of bacterial resistance, with no major change in the overall gut microbiota composition. Antibiotics are therefore modulators of the symbiotic relationship between the host and the gut microbiota. Specific antibiotics, such as rifaximin, can also induce eubiotic changes in the intestinal ecosystem; this additional property may represent a therapeutic advantage in specific clinical settings.

**Key words:** Intestinal bacteria; Antibiotic; Rifaximin; Gut microbiota; Eubiosis; Dysbiosis; Gut microbiota modulation

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**Core tip:** The traditional use of antibiotics in the clinical practice is to antagonize local or systemic infections. However, antibiotics induce several alterations of the

gut microbiota, including the reduction of beneficial bacteria as well as of microbial diversity. Rifaximin is a non-absorbable antibiotic with broad-spectrum activity and non-traditional antimicrobial effects. Rifaximin has the potential to induce a positive modulation of the gut microbiota, favoring the growth of bacteria beneficial to the host without altering its overall composition. Therefore, rifaximin can be defined not only as an antibiotic but also as an “eubiotic”, namely a positive modulator of the gut ecosystem.

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## INTRODUCTION

The human gut microbiota has been the main target of scientific research in the very recent years. Studies based on metagenomic techniques have revealed the multifaceted abilities of gut microbes, ranging from metabolic functions to immunomodulation, from anti-pathogen activity to behavior conditioning<sup>[1-5]</sup>. As the gut microbiota plays a crucial role in maintaining humans’ health, less or more specific gut microbiota alterations have been associated with various gastrointestinal diseases<sup>[6-20]</sup>. These findings strongly support the use of gut microbiota modulators such as antibiotics, prebiotics and probiotics as the treatment of choice in almost all gastrointestinal disorders.

In addition to the speculative and intriguing value of these physiopathological findings, it is also interesting to address which modifications of the gut microbiota may occur after a therapeutic intervention, such as antibiotic treatment. In particular, recent metagenomic studies have highlighted a positive modulation of gut bacteria associated with the administration of rifaximin, one of the antibiotics most frequently used for the treatment of digestive diseases. This has opened the scenario to the new concept of antibiotic-related gut microbiota modulation, which overcomes the traditional bactericidal and bacteriostatic effects and involves the possibility of more complex interactions, resulting in a modulation of the gut flora favorable to the host.

In this paper, we will focus on the effects of antibiotics, and in particular rifaximin, on gut bacteria, discussing both its traditional and non-traditional properties, and defining the new concept of “eubiotic modulation” of the gut microbiota.

## ANTIBIOTICS AND GUT MICROBIOTA

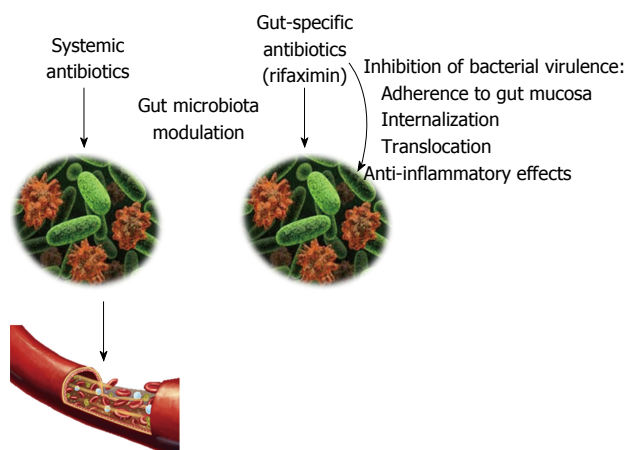
The traditional use of antibiotics in the clinical practice

is to antagonize local or systemic infections. However, after the discovery of the gut microbiota potential, several studies have focused on the effects of antibiotic therapies on commensal gut microbes<sup>[21-27]</sup>. Beta-lactamics, fluoro-quinolones, glycolcyclines, lincosamide, nitroimidazole, and various combinations of antibiotics are able to produce a profound alteration of the gut microbiota composition, mainly characterized by the reduction of autochthonous taxa and by the increase of potentially pathogenic bacteria, such as Enterobacteriaceae. In contrast, *Bifidobacteria*, *Faecalibacterium prausnitzii* and *Lactobacilli*, which usually exert beneficial effects to the gut, seem to be reduced after antibiotic treatment. *Bifidobacteria* are included into several probiotic preparations and have intestinal and systemic anti-inflammatory effects, being also protective against antibiotic associated diarrhea and infective colitis<sup>[28-53]</sup>. *Faecalibacterium prausnitzii* is a butyrate-producing bacterium with a high metabolic activity<sup>[54]</sup>; butyrate is involved in intestinal cells life cycle, has immunomodulatory effects and protects against infections caused by pathogens<sup>[55,56]</sup>. Finally, *Lactobacilli* are known for their anti-inflammatory, immunomodulatory, anti-oxidant, anti-bacterial and anti-viral properties<sup>[57]</sup>.

Besides the effect on specific bacterial strains, antibiotic treatment decreases taxonomic richness, diversity, and evenness of the gut microbial community, producing a shift to an alternative state that is different from the baseline<sup>[27,58]</sup>. These alterations seem to recover after the end of antibiotic administration; however, the gut microbial composition does not exactly return to the pre-treatment condition, but rather it acquires a new connotation, similar (but not identical) to the original one. All these modifications are highly variable among individuals, and the consequences of antibiotics-associated gut microbiota perturbation in humans remain unknown.

Morgun *et al.*<sup>[59]</sup> analyzed metagenomic and metatranscriptomic changes in a mouse model of microbiota depletion after the administration of an antibiotic cocktail (ampicillin, vancomycin, neomycin and metronidazole). The main registered effects, in addition to the drop in total bacterial mass and the emergence of resistant strains, were (1) the impairment of local mucosal immunity, with a depletion of immune cells in the lamina propria and in the villous epithelium, as well as of IgA-producing plasma cells; and (2) mitochondrial toxicity, leading to increased apoptosis and cell death in the intestinal epithelium of treated animals. The authors concluded that gut microbiota depletion as well as the development of resistance among the remaining bacteria and the consequent effects on host tissues were the major consequences produced by antibiotics on the gut.

Therefore, two main properties of antibiotics should be recognized: the classic effect against pathogens, which is the main indication for their use in clinical practice, and the modulation of the commensal gut



**Figure 1** Effects of antibiotics on the gut microbiota. Systemic antibiotics are mainly used to treat extra-intestinal infections but they indirectly affect the gut microbiota composition. Rifaximin is a poorly absorbed antibiotic, exerting its action exclusively in the gastrointestinal tract. In addition to the expected antimicrobial properties, rifaximin inhibits bacterial virulence, down-regulates inflammatory response and has the potential to positively modulate the composition of gut microbial community.

microbiota, which is a “collateral” effect. Although the consequences of this last feature on the host are still not clear, the reduction of beneficial bacteria may cause the loss of the favorable influence exerted by the gut microbiota on human health.

This may reasonably induce to suppose a detrimental effect of antibiotics on intestinal ecology. However, this is not the case of all antibiotics. Recent findings have pointed out that rifaximin can positively modulate the gut microbiota. This peculiar characteristic may differentiate rifaximin from the other systemic antibiotics.

## RIFAXIMIN: A POORLY ABSORBED ANTIBIOTIC WITH NON-TRADITIONAL EFFECTS ON GUT BACTERIA

Rifaximin is an antibiotic with broad-spectrum activity against Gram positive and Gram negative aerobic and anaerobic bacteria, effective for the treatment of travelers’ diarrhea and other gastrointestinal infective conditions such as *Clostridium difficile* colitis<sup>[60-62]</sup>. As a consequence of the negligible systemic absorption (< 0.4%)<sup>[63]</sup>, rifaximin reaches high tissue concentrations, as high as 8000 mcg/g in fecal samples after a 3-d regimen of 800 mg daily<sup>[64]</sup>, far beyond the minimal inhibitory concentrations observed for local microbial isolates. Another characteristic of rifaximin is bile acids-dependent solubility; this makes the drug more effective in the small intestine while colonic bacteria are poorly inhibited<sup>[65]</sup>. Indeed, changes in the colonic gut microbiota composition are progressively but completely reversed after rifaximin interruption, differently from the effects on duodenal bacteria that appear more stable<sup>[66]</sup>.

In addition to the bactericidal and bacteriostatic activity, which is typical of an antibiotic, rifaximin can also exert non-traditional effects on the gut microbiota (Figure 1). In particular, rifaximin can down-regulate the inflammatory response triggered by the gut microbes by inhibiting the activation of the nuclear factor (NF)- $\kappa$ B *via* the pregnane X receptor (PXR) and by reducing the expression of the pro-inflammatory cytokines interleukin (IL)-1B and tumor necrosis factor-alpha (TNF $\alpha$ )<sup>[67-71]</sup>.

Moreover, rifaximin alters bacterial virulence through the inhibition of adhesion, internalization and translocation<sup>[72-75]</sup>, and can modify bacterial metabolism<sup>[76]</sup>.

Rifaximin modulation of gut microbial composition also belongs to the non-traditional features of this poorly absorbed antibiotic.

## EUBIOTIC EFFECTS OF RIFAXIMIN ON THE GUT MICROBIOTA

In addition to the aforementioned activity against bacterial adherence, internalization and translocation and to the anti-inflammatory effects, there is evidence of a positive modulation of the gut microbiota as a consequence of rifaximin treatment (Table 1).

The pioneering study that demonstrated for the first time the increase in beneficial bacterial strains associated with rifaximin intake was conducted more than ten years ago on twelve patients affected by ulcerative colitis<sup>[77]</sup>. Rifaximin was administered at the dose of 1800 mg daily for 3 treatment cycles, each lasting for 10 d, followed by a wash-out period of 25 d. By means of standard bacteriological analysis, the Authors observed an increase in the concentration of *Bifidobacteria* after treatment, which tended to decrease in the interval periods. A subsequent study by the same group using a continuous culture model of the gut microbiota of four patients with active Crohn’s disease (CD)<sup>[78]</sup> also confirmed this preliminary result. Indeed, rifaximin administration at the same dose of 1800 mg daily did not alter the overall composition of the gut microbiota, but promoted the growth of *Bifidobacterium*, *Atopobium* and *Faecalibacterium prausnitzii*.

More recently, Xu *et al.*<sup>[79]</sup> demonstrated that *Lactobacilli* could grow in response to rifaximin administration. In particular, in the mouse model of visceral hyperalgesia used in the study, the administration of rifaximin increased the abundance of *Lactobacilli* in the ileum; this effect was restricted only to this antibiotic, since in the same experimental conditions the administration of another poorly absorbed antibiotic, neomycin, produced just an increase in Proteobacteria.

Finally, two metagenomic analyses of the gut microbiota of human subjects affected by gastrointestinal and liver diseases have been recently

Table 1 Studies investigating the effects of rifaximin on gut microbiota composition

Ref.	Patients/model	Technique	Rifaximin dose	Changes in gut microbiota after rifaximin
Brigidi <i>et al</i> <sup>[77]</sup> , 2002	12 pts UC	Standard bacteriological procedures	1800 mg/d, 3 cycles of 10 d followed by 25 d of wash-out	<i>Enterococci</i> : < <i>Coliform</i> : = <i>Bifidobacteria</i> : > <i>Lactobacilli</i> : < <i>Clostridium perfringens</i> : > than < <i>Bacteroides</i> : unpredictable variations <i>Candida</i> : = Overall composition: not explored <i>Bifidobacterium</i> : > <i>Atopobium</i> : >
Maccaferri <i>et al</i> <sup>[78]</sup> , 2010	4 pts colonic active CD	Continuous culture colonic model system, FISH, quantitative PCR, PCR-denaturing gradient gel electrophoresis	1800 mg/d	<i>Faecalibacterium prausnitzii</i> : > Overall composition: =
Bajaj <i>et al</i> <sup>[76]</sup> , 2013 Xu <i>et al</i> <sup>[79]</sup> , 2014	20 pts HE Rat model of visceral hyperalgesia	454 pyrosequencing Quantitative PCR, 454 pyrosequencing	1100 mg/d 150 mg/kg, twice daily	Overall composition: = <i>Lactobacillus</i> : > Clostridiaceae, Erysipelotrichaceae, and Peptostreptococcaceae: < Overall composition: 84% reduction in bacterial load
Soldi <i>et al</i> <sup>[80]</sup> , 2015	15 pts non-C IBS	Real-time PCR, Illumina pyrosequencing	1650 mg/d for 14 d	<i>Faecalibacterium prausnitzii</i> : > Clostridiaceae, Streptococcaceae: < Bacteroidaceae, Prevotellaceae: > Overall composition: =
Ponziani <i>et al</i> <sup>[81]</sup> , 2016	20 pts CD, UC, non-C IBS, DD, HE	454 pyrosequencing	1200 mg/d for 14 d	<i>Lactobacillus</i> : > <i>Roseburia</i> , <i>Haemophilus</i> , <i>Veillonella</i> and <i>Streptococcus</i> : < Overall composition: =

Pts: Patients; UC: Ulcerative colitis; CD: Crohn's disease; FISH: Fluorescence in situ hybridization; PCR: Polymerase chain reaction; HE: Cirrhosis with hepatic encephalopathy; non-C IBS: Irritable bowel syndrome without constipation; DD: Diverticular disease.

published.

In the first one<sup>[80]</sup>, patients with non-constipated irritable bowel syndrome were treated with rifaximin 550 mg tid for 14 d. Fecal specimens were collected before starting the treatment, at the end of it, and after a 6-wk wash-out period. As one of the most intriguing result of the study, the Authors observed an increase in *Faecalibacterium prausnitzii* abundance at the end of treatment, without any major modification of the overall gut microbiota composition.

In the second study<sup>[81]</sup>, rifaximin was administered at the dose of 1200 mg daily for 10 d to patients with different gastrointestinal diseases, including irritable bowel syndrome, CD, ulcerative colitis and diverticular disease, and also to patients with liver cirrhosis complicated by hepatic encephalopathy. Stool samples were analyzed before, at the end and 1 mo after the end of rifaximin treatment. *Lactobacillus* abundance was increased at the end of treatment with rifaximin and 1 mo thereafter, while no modification of the overall composition of the gut microbiota was observed, even stratifying patients according to treatment timepoints and considering the original disease.

In conclusion, rifaximin is able to increase the abundance of beneficial intestinal bacteria, while

keeping stable the overall composition of the gut microbial community. Although this peculiar behavior has been described so far only in association with rifaximin, it is related to one of the most common consequences of antibiotic therapies: the development of microbial resistance. Indeed, members of *Bifidobacterium*, *Lactobacillus*, *Bacteroides*, *Clostridium*, *Eubacterium*, *Atopobium* and *Collinsella* genera may develop mechanisms of resistance after rifaximin exposure, becoming able to grow at rifaximin concentrations higher than 1024 mg/L<sup>[82,83]</sup>.

In the previously reported study, Brigidi *et al*<sup>[77]</sup> demonstrated that the increase in Bifidobacteria consequent to rifaximin intervention was associated with the increase of minimal inhibitory concentrations (MIC) values from 16 mcg/mL to 40 mcg/mL. Notably, rifaximin inhibits bacterial RNA synthesis acting on the  $\beta$  subunit of the RNA polymerase, and missense mutations of the core region of the *rpoB* gene encoding the  $\beta$  subunit of RNA polymerase have been described in *Bifidobacterium infantis* following rifaximin exposure<sup>[84,85]</sup>. Therefore, in the case of rifaximin, the acquisition of resistance may represent an advantage for the host rather than a detrimental consequence. However, the development of rifaximin resistance requires chromosomal mutation, which

is vertically transmitted and has, therefore, a rare diffusion among intestinal microorganisms<sup>[61]</sup>; as a consequence, almost all resistant bacteria disappear within weeks after treatment discontinuation<sup>[86]</sup>. Data from metagenomic studies reflect this characteristic. Indeed, immediately after the beginning of rifaximin treatment, bacterial alpha diversity shows a trend towards reduction, reverting to values similar to pre-treatment after a wash-out period<sup>[80,81]</sup>.

Based on these considerations, and also on the preliminary evidence that rifaximin effects do not abruptly disappear after treatment interruption, lasting in the short time period, further studies are needed to investigate if the positive modulation of the gut microbiota produced by rifaximin could persist over time.

## RIFAXIMIN AS EUBIOTIC AGENT IN CLINICAL PRACTICE

In addition to the favorable modulation of the gut microbiota, rifaximin presents other features that make its use safely applicable in clinical practice.

Rifaximin is poorly absorbed and a negligible concentration is retrieved in urine after oral administration. This feature is typical of the branded formulation of the drug, which contains only the crystal polymorph  $\alpha$ , while a higher systemic bioavailability has been demonstrated for the generic formulation containing an amorphous form of the molecule<sup>[87]</sup>. Considerations about careful use of rifaximin in conditions increasing intestinal permeability, such as liver impairment, should also be provided. Rifaximin systemic exposure is increased by 10, 13 and 20 folds in Child A, B and C cirrhotic patients, respectively; although no dose adjustment is required by the manufacturer, a careful use is advisable in this clinical setting<sup>[88]</sup>.

Rifaximin drug interactions are also expected to be rare, as confirmed by two studies including healthy individuals on treatment with CYP450 substrates<sup>[89,90]</sup>. P-glycoprotein is also involved in the metabolism of rifaximin but the clinical consequences of the co-administration of p-glycoprotein inhibitors are unknown.

Rifaximin has also been safely used in elderly subjects<sup>[91]</sup> and children<sup>[92]</sup>. However, teratogenic effects on the fetus have been demonstrated in animal models, and the benefits of rifaximin in pregnant women should be weighed against this risk<sup>[88]</sup>.

A final consideration should be drawn about rifaximin tolerability in clinical practice. In the major studies reporting on rifaximin use in gastrointestinal diseases and hepatic encephalopathy, a low rate of adverse events has been registered, mainly of mild/low grade and with a similar frequency compared to the placebo<sup>[93]</sup>. The most frequent ones have been headache, nausea, dizziness, dyspepsia, abdominal discomfort, abdominal distention, diarrhea, constipation

and flatulence. The incidence of infections was low too, and the few cases of *C. difficile* colitis reported during rifaximin treatment were generally associated with predisposing conditions, such as hospitalization and prolonged antibiotic use.

Therefore, rifaximin eubiotic properties are associated with a good safety and tolerability profile, which makes possible a wide use of this molecule in different clinical settings.

## EUBIOSIS: A NEW-OLD CONCEPT

The increase in bacteria beneficial to the gut associated with rifaximin treatment, together with its additional properties and its local action, reasonably support a reclassification of this molecule, which can be defined not only as an antibiotic but also as an "eubiotic", namely a positive modulator of the gut ecosystem.

Usually, humans live in a commensal and mutualistic symbiotic relationship with their own gut microbiota, which is a prolonged and close association resulting in a benefit for one or both the organisms<sup>[94]</sup>.

However, the term "symbiosis" does not completely describe the exact nature of this cooperation, failing to depict the dynamism that is the culprit of this relationship. Indeed, while the human host can be considered a relatively stable system, it is extremely difficult to take a static picture of the gut microbiota. However, trying to partially summarize the high variability of the microbial ecosystem, two main conditions may be outlined: "dysbiosis" and "eubiosis". Dysbiosis has been defined as a condition characterized by "imbalanced intestinal microbial community with quantitative and qualitative changes in the composition of the microbiota itself, in its metabolic activities or in the local distribution of its members"<sup>[94]</sup>; in contrast, a proper definition of eubiosis has not been provided yet. Intuitively, a quantitative and qualitative harmonic balance of the gut microbial components, resulting in a healthy metabolic and immunologic cooperation with the host, should be the main feature of eubiosis. However, apart from infections caused by opportunistic and non-opportunistic pathogens, it is difficult to figure-out which could be the main change conditioning the transition from eubiosis to dysbiosis in other pathologic settings (*e.g.*, irritable bowel syndrome, inflammatory bowel diseases *etc.*). Probably dysbiosis may occur transiently in healthy individuals, usually resolving spontaneously without any clinical manifestation or presenting with mild symptoms. Conversely, changes in the composition of the gut microbiota observed in patients with gastrointestinal diseases may be configured as a the persistence of dysbiotic alterations that fails to recover, thus contributing to the onset and to the progression of the pathologic condition in predisposed individuals, as well as to the worsening of clinical symptoms. This explains the efficacy of eubiotic compounds such as rifaximin in

these clinical settings: the beneficial modulation of the gut microbiota produced by rifaximin, together with its other non-traditional effects, result in a beneficial anti-inflammatory and trophic action on the intestine.

## CONCLUSION

The symbiotic host-gut microbiota relationship is a condition of relational harmony fluctuating between eubiosis and dysbiosis. Since dysbiosis plays a role in the pathogenesis and in the progression of several gastrointestinal and systemic diseases, the use of eubiotics, such as rifaximin, should be reconsidered in these settings in the light of the positive modulating effects on the gut microbial community, and their use should be further supported and integrated with the other available medical treatments.

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