



REVIEW

The Intestinal Microbiota as a Reservoir and a Therapeutic Target to Fight Multi-Drug-Resistant Bacteria: A Narrative Review of the Literature

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ABSTRACT

The appearance and dissemination of antibiotic-resistant bacteria, particularly in specific closed environments such as intensive care units of acute care hospitals, have become a major health concern. The intestinal microbiota has various functions including host protection from overgrowth or colonization by unwanted bacteria. The exposure to antibiotics significantly reduces the bacterial density of intestinal microbiota leaving an ecologic void that can be

occupied by potentially pathogenic and/or resistant bacteria frequently present in hospital settings. Consequently, the intestinal microbiota of inpatients acts as a major reservoir and plays a critical role in perpetuating the spread of resistant bacteria. There are novel innovative methods to protect the host microbiota during antibiotic treatment, but they do not offer a solution for already established colonization by resistant microorganisms. Fecal microbiota transfer (FMT) is a promising intervention to achieve this goal; however, controlled trials report lower success rates than initial retrospective studies, especially in case of gram negatives. The aim of the present article is to highlight the importance of the intestinal microbiota in the global spread of multi-drug-resistant (MDR) microorganisms and to review the recent advances to protect the human microbiota from the action of antibiotics as well as a critical discussion about the evidence of decolonization of MDR microorganisms by FMT.

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Key Summary Points

The human gut acts as a major reservoir of MDR bacteria, where they overgrow and share genetic determinants of resistance with other species, perpetuating their spread.

The most common strategy for gut decolonization is the use of oral, non-absorbable antibiotics, although fecal microbiota transference (FMT) is a promising intervention.

We summarize 145 FMTs performed for intestinal decolonization of MDR bacteria in the last 5 years from 25 publications.

According to our analysis, FMT was significantly more successful against GPC than GNB, with no antibiotic consumption after FMT in the case of concomitant CDI and in older versus recent reports.

INTRODUCTION

Antibiotic treatment has significantly improved the outcome of infected patients and has significantly reduced the number of surgical infections. Bacteria are considered multi-drug resistant (MDR) when they become resistant to at least 1 agent in ≥ 3 antibiotic classes to which they are normally expected to be susceptible. During the last 15 years, the spread of genetic determinants of resistance has led to the emergence of extensively drug-resistant (resistant to at least 1 agent in all but ≤ 2 antibiotic classes) and pandrug-resistant bacteria (resistant to all agents in all antibiotic classes) [1]. Although some resistant bacteria are present in the community, the majority are found in hospitals where these bacteria find susceptible hosts but also the perfect environment to spread through the activity of health care workers. The most relevant MDR gram

negatives include third-generation cephalosporin-resistant (3GCR) and carbapenem-resistant (CR) Enterobacterales, CR *Acinetobacter baumannii* and CR *Pseudomonas aeruginosa* [2]. These pathogens are associated with severe infections including ventilator-associated pneumonia, catheter-related bacteremia and surgical site infections that have a significantly higher morbidity and mortality than those caused by the same susceptible species [3–5]. Hand hygiene, isolation precautions [6], antibiotic stewardship programs [7] and decolonization with non-absorbable antibiotics [8] have proved to be only partially effective to diminish the spread of MDR microorganisms.

In this context, it is evident that alternative methods to combat the spread of MDR bacteria are warranted. The human gut contains > 100 million bacteria that play an important role in metabolic processes, immune modulation and protection against the colonization or overgrowth of pathogenic microorganisms (colonization resistance). A dysbiotic microbiota is an imbalance in the intestinal microbial community (including bacteria, yeast, viruses and parasites) characterized by quantitative and qualitative changes in the composition of the microbiota itself, which entails a loss of its functions [9]. *Clostridioides difficile* infection (CDI), the most common cause of diarrhea in hospitalized patients, is the consequence of antibiotic-induced dysbiosis [10]. The lack of microbiota recovery after an episode of diarrhea is associated with recurrent episodes and has been successfully treated with fecal microbiota transfer (FMT) from healthy volunteers. Whether this therapeutic approach can be applied to other entities related to dysbiosis is under debate [11].

The objective of this narrative review is to discuss the importance of intestinal microbiota as a reservoir of MDR pathogens and review original strategies that aim to preserve and/or modulate the composition of intestinal microbiota, with special focus on FMT. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

INTESTINAL MICROBIOTA AS A RESERVOIR FOR MDR GRAM NEGATIVES AND FACTORS ASSOCIATED WITH PERSISTENT CARRIAGE

The worldwide spread of 3GCR Enterobacterales has led to a significant increase of carbapenem prescription in the last decade, which, in turn, has greatly contributed to the recent emergence of CR gram-negative bacteria. Currently, in Europe, one out of every three *Klebsiella pneumoniae* isolates is resistant to third-generation cephalosporins, and one-third of these strains have additional resistance to fluoroquinolones and aminoglycosides as well. The mean prevalence of CR *K. pneumoniae* is 7.2%, but this percentage is as high as 29% in Italy and 64% in Greece [12]. The prevalence of 3GCR and CR Enterobacterales in inpatients from the USA is 12.6% and 1.2%, respectively [13]. In addition, the problem of MDR in other gram negatives such as *A. baumannii* and *P. aeruginosa* is a major concern in intensive care units worldwide with percentages of carbapenem resistance > 20% [14].

The presence of MDR bacteria was initially associated with acute care hospitals; however, with the increased survival of susceptible patient populations in the Western world, the problem has been extended to rehabilitation centers and nursing homes in recent years, converting these into major sources of patients colonized with MDR bacteria [15]. Interestingly, the MDR Enterobacterales in Europe and America remain confined to the health care-related population, while the gut colonization in the community is < 5%. However, in Africa and Asia this percentage increases up to 15% and 46%, respectively [16], suggesting that MDR bacteria are able to colonize even healthy people if the exposure, usually from contaminated foods [17, 18], is high enough. As a consequence, traveling to certain developing countries is a risk factor for MDR bacteria acquisition [19]. Two prospective trials [20, 21] followed > 2500 returned European travelers for a year, and the pooled median duration of post-travel colonization was 30 days [22]. In contrast, in

another European study, the percentage of persistent carbapenemase-producing *K. pneumoniae* carriers at 6, 12 and 24 months after discharge from an acute-care hospital was 55%, 30% and 20%, respectively. The main risk factors for being a persistent carrier were the presence of any catheter, living in a long-term care facility, a low functional status measured by Barthel's index and important comorbidity according to Charlson's score [23]. The conclusion from these results is that under high exposure to MDR gram negatives (Asia, Africa), healthy people may be transiently colonized, but once the exposure disappears, the microbiota is able to avoid the definitive engraftment of these microorganisms. In contrast, "fragile" patients (older, with comorbidities) [24] have been associated with a dysbiotic microbiota [25] that is aggravated by antibiotic consumption, which favors prolong colonization.

On the other hand, the number of new antibiotics has dropped considerably in recent years, and there are hardly any novel antibiotic classes on the horizon (Fig. 1). Consequently, the above situation gave rise to the renaissance of the utilization of the highly toxic colistin, which promptly brought about the appearance of a new type of colistin resistance that may pose a severe public health threat in the next years [26].

The intestine harbors one of the most important microbial communities of the human body regarding microbial density and diversity [27]. The intestinal microbiota is implicated in different physiologic processes that are essential to the host health. One of these processes is colonization resistance, which consists of the gut microbiota's ability to avoid intestinal pathogen or MDR bacteria colonization by directly competing for the ecologic niche with these microorganisms or indirectly stimulating the human immune defenses [28]. One example of the colonization resistance mechanism is the butyrate-producing obligate anaerobe members of the Firmicutes and Bacteroidetes phyla, a major and critical component of the intestinal microbiota. Microbially produced butyrate promotes local immune system homeostasis, gut epithelial barrier function, proliferation of health-associated

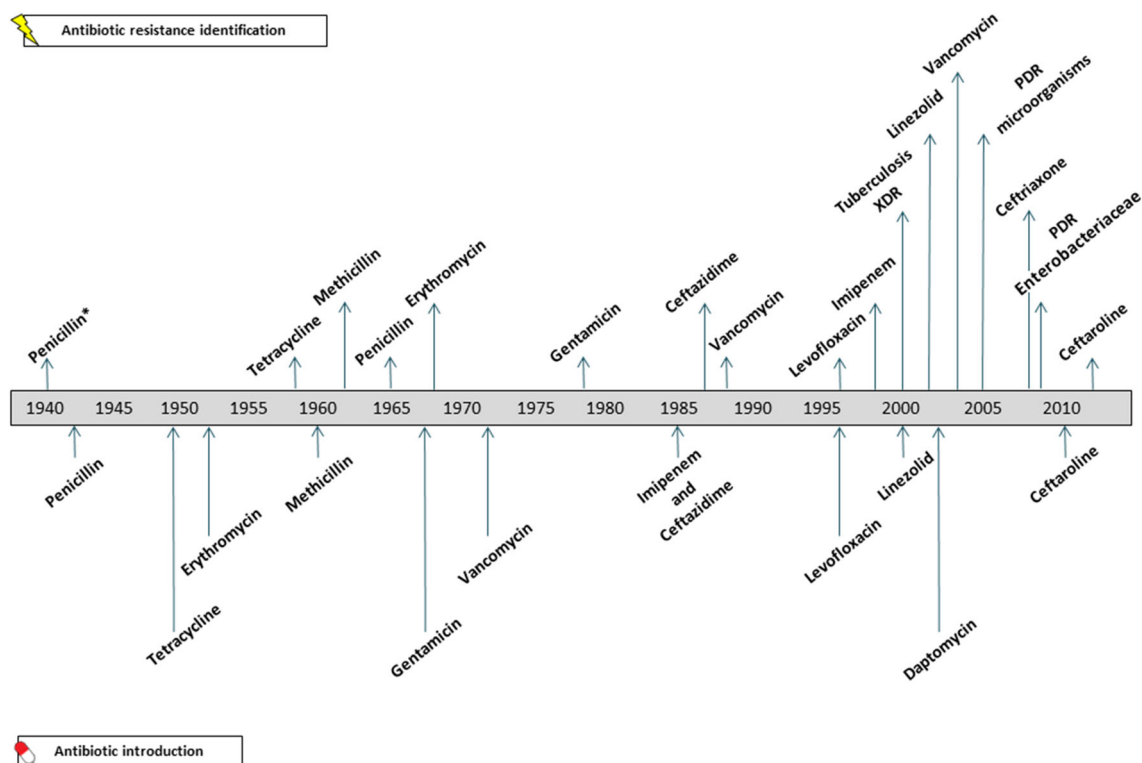


Fig. 1 Year of commercialization of the principal antibiotics and time of first detection of resistant strains. *XDR* extensively drug resistant, *PDR* pandrug resistant.

*Described in *Staphylococcus*. (Adapted from <https://www.cdc.gov/drugresistance/about.html>)

anaerobes and suppression of facultative anaerobes such as Enterobacterales [29]. Administration of antimicrobial agents is one of the main causes of intestinal microbiota disturbances that can lead to dysbiosis (see definition above). The intensity of the microbiota damage induced by antibiotic consumption and consequently the risk of dysbiosis depends on: (1) the active antibiotic concentration in feces, which is related to the dose, route of administration, oral bioavailability, bile elimination and potential in vivo inactivation, (2) antibiotic spectrum and (3) exposure duration [30]. However, the intestinal microbiota has the ability to restore its equilibrium after an external perturbation (i.e., antibiotic treatment) known as the resilience phenomenon [31], which varies from one individual to another, suggesting that the risk of developing dysbiosis also depends on the diversity and specific composition of the intestinal microbiota of each individual [32].

During a state of dysbiosis, the niches that are left open after disturbances can be occupied by the overgrowth of microorganisms that at low densities are symbionts but have pathogenic potential at high densities (pathobionts). Members of the phylum Proteobacteria (*Escherichia coli* or *K. pneumoniae*) normally represent < 2% of the microbiota, but in dysbiotic state these bacteria can represent > 30% of the total species. On the other hand, through health care workers' hands as a vector of transmission, this ecologic void can be occupied by environmental opportunistic pathogens (*K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *S. maltophilia*) that frequently carry genetic determinants of resistance in a hospital setting. Additionally, considering that the intestine also provides an optimal environment for horizontal gene transfer between microbes, exchange of resistance determinants is also favored [33]. From this perspective, the dysbiotic microbiota is a key factor (reservoir) to perpetuate the

spread of MDR gram negatives. In recent years, oral beta-lactamases and products that absorb antibiotics in the proximal colon have been developed to minimize the deleterious effect of antibiotics on intestinal microbiota [34–36].

BENEFIT OF ERADICATION OR REDUCTION IN THE PREDOMINANCE OF MDR GRAM NEGATIVES IN THE INTESTINAL MICROBIOTA

On the one hand, intestinal colonization by MDR bacteria in hospitalized patients increases the risk of dissemination of the bacteria in the ward. On the other hand, it increases the risk of an infection by the same bacteria. As mentioned before, Proteobacteria normally represent < 2% of the microbiota, but a longitudinal study in patients undergoing allogeneic hematopoietic stem cell transplantation demonstrated marked shifts in bacterial populations inhabiting the gut. Intestinal domination, defined as occupation of at least 30% of the microbiota by a single predominating bacterial taxon, occurred frequently. Commonly encountered dominating organisms included *Enterococcus*, *Streptococcus* and various Proteobacteria. Enterococcal and proteobacterial domination increased the risk of *Enterococcus* spp. and gram-negative rod bacteremia nine- and fivefold, respectively [37].

The most common strategy for gut decolonization is the use of oral, non-absorbable antibiotics, which may reach sufficiently high concentrations in the digestive tube to inhibit bacterial growth [38, 39]. A recent retrospective study on patients colonized by carbapenemase-producing *K. pneumoniae* showed that oral aminoglycoside reduced the risk of being infected by the same colonizing *K. pneumoniae* by > 80% and also reduced the mortality rate [40]. Interestingly, these differences were achieved although the microbiologic eradication (two consecutive negative rectal swabs) was only obtained in 59% of the treated cases. This great impact suggests that it is not necessary to eradicate the microorganism but to reduce its density to exert a benefit on the patients'

outcome. We do not know what the impact of density reduction on the bacterial dissemination is, but it seems reasonable to also expect a positive effect. The major concern of this study is that there were significantly more gentamicin-resistant microorganisms detected in treated patients than in the control group (13.6% vs. 3%, $p = 0.008$) [40]. Similarly, the appearance of resistance in gram-negative bacteria was also observed after topical administration of colistin [41]. Additionally, non-absorbable antibiotics inevitably perpetuate intestinal dysbiosis. Therefore, it is of paramount importance to find alternative solutions to eradicate or reduce the density of MDR bacteria in the gut of colonized patients and restore a healthy microbiota composition in these patients.

FECAL MICROBIOTA TRANSFER

FMT from a healthy donor is a well-recognized treatment of multiple recurrences of CDI where the fundamental underlying problem is a severe dysbiosis [10]. Classically, this procedure has been named fecal microbiota transplantation. However, the intestinal microbiota is not an organ like the liver or kidney. We consider that transfer is a more adequate designation. The aim of this section is to review the published experience on using FMT for intestinal decolonization of MDR microorganisms.

We conducted a literature search in PubMed using the following keywords: fecal microbiota transplantation, gut microbiota, multi-drug-resistant microorganisms and gut, but we found more articles by reviewing the literature. Revision articles, duplications of the same data and articles where the end point was not clearly decolonization rate were excluded [42–44]. We identified 25 publications that summarize 145 FMTs performed in MDR bacteria-carrying patients in the last 5 years (Table 1). Fourteen of these publications were case reports ($n = 17$), three articles described retrospective cohorts ($n = 29$), and eight publications reported prospective data, mostly uncontrolled trials ($n = 99$). Of the reported 145 cases, 39 (26.9%) corresponded to patients colonized by a MDR microorganism and a concomitant CDI. Forty-

Table 1 Published experience on the efficacy of FMT in the decolonization of multi-drug resistant microorganisms

Study	Publication type	MDR bacteria	Concomitant CDI	Length of follow-up (days)	Eradication rate (<i>n/N</i> , %)
Freedman [49]	Case report	KPC-KP	No	240	1/1, 100%
Singh [50]	Case report	ESBL-EC	No	84	1/1, 100%
Jang [51]	Case report	VRE	Yes	90	1/1, 100%
Crum-Cianflone [52]	Case report	CR-KP, -PA, -AB, MRSA, VRE	Yes	105	1/1, 100%
Stripling [53]	Case report	VRE	Yes	365	1/1, 100%
Lagier [54]	Case report	OXA-48-KP	No	14	1/1, 100%
Lombardo [55] ^a	Prospective trial	VRE	Yes	28	8/8, 100%
Wei [56]	Prospective trial	MRSA	No	90	5/5, 100%
Bilinski [57]	Case report	NDM-KP, ESBL-EC	No	26	1/1, 100%
García-Fernandez [58]	Case report	VIM-1-KP	Yes	180	1/1, 100%
Eysenbach [59]	Retrospective study	VRE	Yes	42	9/9, 100%
Dubberke [60]	Prospective trial	VRE	Yes	180	8/10 ^b , 80.0%
Sohn [61]	Case report	VRE	In two of the three cases	70–147	1/3, 33.3%
Stalenhoef [62]	Case report	ESBL-EC	No	90	0/1, 0%
Ponte [63]	Case report	CR-KP	Yes	100	1/1, 100%
Davido [64]	Prospective trial	OXA-48-KP (4); VRE(2); NDM-KP (1); OXA-48-KP, EC (1)	No	90	3/8, 37.5%

Table 1 continued

Study	Publication type	MDR bacteria	Concomitant CDI	Length of follow-up (days)	Eradication rate (n/N, %)
Bilinski [46]	Prospective trial	NDM-KP, ESBL-EC (6); NDM-KP (5); NDM-KP, ESBL-EC, VRE (1); NDM-KP, ESBL-EC, CR-PA, VRE (1); ESBL-KP (1); ESBL-EC (1); ESBL-KP, EC (1); CR-KP, MBL-PA (1); CR-KP, <i>S. maltophilia</i> (1); CR-KP, ESBL-KP, EC, MBL- <i>A. uuringii</i> (1); CR- <i>E. cloacae</i> , <i>S. maltophilia</i> (1); MBL-PA (1); CR-PA (1); OXA-48-EC (1)	In one of the 23 cases ^c	30	15/23, 65.2%
Lahtinen [65]	Case report	ESBL-EC	No	42	1/1, 100%
Innes [66]	Case report	GES-5-KP, ESBL-EC	Yes	100	1/1, 100%
Singh [67]	Prospective trial	ESBL-EC (12); ESBL-KP (2); ESBL-EC, -KP (1)	No	28	6/15, 40%
Dias [68]	Case report	CR- <i>Enterobacteriales</i>	Yes	90	2/2, 100%
Davido [69]	Prospective trial	VRE (8)	No	90	7/8, 87.5%
Saidani [48]	Retrospective study	Oxa-48-KP (4); NDM-KP (2); OXA-48-KP, EC, <i>E. cloacae</i> (1); OXA-48-KP, EC, <i>S. marcescens</i> (1); OXA-24-AB (1); OXA-48- <i>C. koserii</i> , <i>C. freundii</i> (1)	No	14–180	8/10, 80%
Huttner [47]	Prospective trial	ESBL-EC (9); ESBL-KP (3); ESBL-KP, OXA-48-EC (2); OXA-48-EC (1); ESBL- <i>E. cloacae</i> (1); ESBL-KP, EC (1); ESBL-EC, <i>E. cloacae</i> (1); NDM-EC, <i>C. freundii</i> (1); ESBL-KP, NDM-EC (1); OXA-48-KP, ESBL-EC (1)	No	150–210	14/21, 66.6%
Battipaglia [70]	Retrospective study	CR-PA (2); CR-PA, ESBL- <i>Enterobacteriales</i> (2); CR- <i>Enterobacteriales</i> , ESBL- <i>Enterobacteriales</i> (2); VRE, ESBL- <i>Enterobacteriales</i> (2); CR- <i>Enterobacteriales</i> (1); CR-KP, <i>E. cloacae</i> , <i>C. freundii</i> (1)	No	33–1220	4/10, 40%

KP *Klebsiella pneumoniae*, EC *E. coli*, VRE vancomycin-resistant *Enterococcus*, CR carbapenem resistant, PA *P. aeruginosa*, AB *A. baumannii*, MRSA methicillin-resistant *S. aureus*, MBL metallo-beta-lactamase

^a SER-109 is an encapsulated, frozen, feces-derived product consisting of the spores of 50 species of the Firmicutes phylum

^b Eleven patients were treated; in one patient treatment success could not be determined because of the the patient's death from an unrelated cause during follow-up

^c There were 25 FMTs in 20 patients. Two of the second FMTs were performed within 30 days after the first ones and were not considered separate colonization episodes in our study

Table 2 Decolonization rate according to different sub-groups among the MDR-colonized patients who underwent an FMT and in whom the outcome was available (N = 144)

Sub-group ^a	Success (n = 101) ^b n/ N (%)	Failure (n = 43) ^b n/ N (%)	p ^c
Female sex	26/60 (43.3%)	16/34 (47.1%)	0.830
Age in years	56.5 (44.3–68)	61.0 (42–70)	0.309
Gram-positive cocci (GPC)	44/101 (43.6%)	8/43 (18.6%)	0.004
Gram-negative bacilli (GNB)	60/101 (59.4%)	37/43 (86.0%)	0.002
Carbapenem-resistant GNB	39/60 (65.0%)	20/37 (54.1%)	0.294
Concomitant <i>C. difficile</i> infection	35/101 (34.7%)	3/43 (7.0%)	< 0.001
Related donor	13/88 (14.8%)	6/43 (14.0%)	1.000
Female donor	10/31 (32.3%)	3/18 (16.7%)	0.322
FMT with frozen microbiota	42/78 (53.8%)	17/39 (43.6%)	0.331
Feces quantity (g)	50 (50, 150)	73.5 (50, 150)	0.121
Upper gastrointestinal tract administration (oral, nasogastric tube or gastroscopy)	74/89 (83.1%)	34/43 (79.1%)	0.632
More than one FMT	29/101 (28.7%)	15/43 (34.9%)	0.554
Prospective trial	66/101 (65.3%)	32/43 (74.4%)	0.333
Study year 2017–2019 vs. 2014–2016	62/101 (61.4%)	39/43 (90.7%)	< 0.001

Significance was considered when *p* value < 0.05 is shown in bold

^a Discrete variables are expressed in proportion and percentage, continuous variables as a median and interquartile range

^b Sum of the total number of the denominators (*N*) in each row does not always equal 145 because in some articles the information was not available

^c *p* values were determined by Fisher's exact test for discrete variables and Mann-Whitney *U* test for continuous variables

eight FMTs (33.1%) were performed in patients carrying MDR gram-positive cocci (GPC), 92 (63.4%) in carriers of gram-negative bacilli (GNB) and 5 in patients colonized by both GPC and GNB (3.4%). Of the 97 GNB colonizations, 59 (60.8%) were due to carbapenem-resistant strains.

Demographic data and technical details of FMT were not available in all publications; for this reason we provide the numerator and denominator of each characteristic. Based on available data, 42/94 (44.7%) of FMT recipients were female, with a median age of 59 (IQR 43.5–70) years. Donors were unrelated in 113/132 studies (85.6%), and the gender was available in only 49, with 26.5% (13/49) being female. FMT was performed using a fresh

donation in 49.1% (53/108) and frozen microbiota in 50.9% (55/108) of the cases. The median amount of feces used for FMT was 50 g (IQR 50–150 g). More patients received the FMT through a nasogastric tube (80/145, 61.9%) than by the oral route (24/145, 17.9%) or enema (22/145, 16.4%). Additionally, in three patients FMT was administered via colonoscopy (2.2%), in each case (0.7%) via gastroscopy or a combination of enema and nasogastric tube. On 101 occasions (69.7%), a single FMT was performed, while 2, 3 and 4 FMTs were performed in 37 (25.5%), 5 (3.4%) and 2 cases (1.4%), respectively.

The criterion for success differed between studies, but was based on a certain number of negative follow-up rectal swabs in most cases.

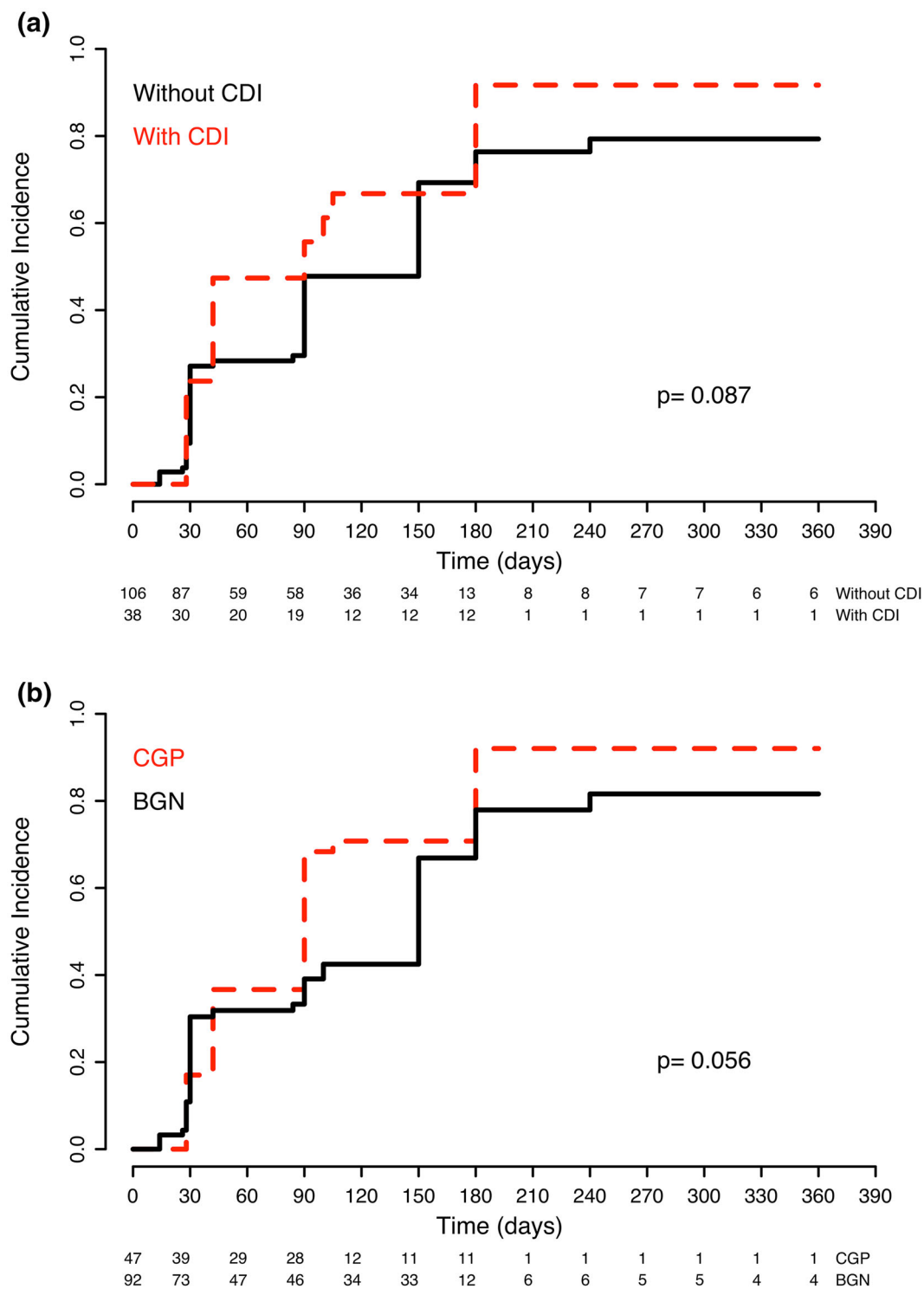


Fig. 2 Cumulative incidence of MDR bacteria decolonization according to concomitant CDI and type of bacteria (p value according to log-rank test). **a** MDR

bacteria decolonization according to the presence of concomitant CDI. **b** MDR bacteria decolonization according to gram staining of the colonizing MDR

Median follow-up time was 90 days (IQR 30–150 days, range 14–1220 days). Overall success rate was 70.1% (101/144). Table 2 summarizes the comparison of successful and failed FMTs according to relevant characteristics. The main findings were that FMT was significantly more successful: (1) against GPC than GNB, (2) in the case of concomitant CDI, (3) in older reports (2014–2016 vs. 2017–2019) and (4) when no antibiotic was given after FMT.

The temporal difference could be attributed to the fact that GPC colonization and concomitant CDI were more frequent in older studies (mostly case reports and retrospective cohorts) while most recent publications were prospective trials. However, the type of microorganism and concomitant CDI remained statistically significant for outcome even when limiting the analysis to prospective trials. The success rate in GNB colonization was 56.9% vs. 87.9% in GPC ($p = 0.003$) and 89.5% in the case of concomitant CDI vs. 62.0% in its absence ($p = 0.028$). In both situations, decolonization also tended to be achieved earlier (Fig. 2). The explanation for better results in GPC (mainly *Enterococcus* spp.) is not evident, but a recent animal model demonstrated that predominance of ampicillin-resistant enterococci induced by ampicillin can be cleared by using a simple combination of four species (*Clostridium bolteae*, *Blautia producta*, *Bacteroides sartorii* and *Parabacteroides distasonis*) [45]. We hypothesize that greater diversity in the donor microbiota increases its competitive ability and clearing of GNB. Indeed, one of the largest studies focusing on GNB showed that donor microbiota richness and biodiversity were significantly associated with gut decolonization [46]. As mentioned, also concomitant CDI was associated with a higher decolonization rate after FMT, suggesting that the deeper the dysbiosis, the easier the donor microbiota engraftment and displacement of MDR bacteria. In line with this, it has been suggested that intestinal preparation before FMT reduces the bacterial content in the gut lumen and enhances engraftment of the microbiota transferred [47, 48].

Taken together, the data support that the decolonization of MDR-GNB using FMT needs to be tuned more finely to obtain better results.

Based on evidence from CDI, colonoscopic administration of fresh microbiota obtained from 50 g of feces of a healthy donor is associated with the highest efficacy. To improve decolonization of GNB by FMT, we suggest the following: (1) to select donors with rich and diverse microbiota, (2) to reduce the host microbiota by bowel preparation as we do before a colonoscopy and to give non-absorbable antibiotics before FMT and (3) to increase the microbiota dose, particularly among patients without CDI and those who receive antibiotics after FMT. In these patients it may be necessary to increase the total amount of microbiota by multiple FMTs in short periods of time or by repeating FMT every time the patient receives an antibiotic. Alternatively, the impact of FMT may be increased by multiple capsules containing a high microbiota concentrate (e.g., by lyophilization) several times. In the future, it will be necessary to promote prospective studies to evaluate each of these proposals.

CONCLUSION

The rise of MDR bacteria is a growing global threat. The intestinal microbiota of patients acts as a major reservoir where these bacteria overgrow, dominate and share genetic determinants of resistance with other strains and species, thus perpetuating the spread of MDR bacteria. There are novel innovative methods to protect host microbiota during antibiotic treatment, but they do not offer a solution for established MDR colonization. FMT is a promising intervention to achieve this goal, although recent controlled trials report lower success rates than initial retrospective studies, especially in the case of GNB. It seems that microbiota engraftment and clearance of MDR GNB are favored by a profound host dysbiosis as in the case of CDI, whereas in other situations the results of FMT are only modest. Apparently, improved protocols need to be adapted for different clinical situations. Well-designed prospective trials addressing individual details of the procedure are needed to elucidate this complex issue.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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