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Original Research Article

Frequency and associated factors for carbapenem-non-susceptible *Bacteroides fragilis* group bacteria colonization in hospitalized patients: Case control study in a university hospital in Turkey

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ABSTRACT

Purpuse: The carbapenem-resistant *Bacteroides fragilis* group (CR-BFG) bacteria have been reported in several countries recently with increasing global attention. The high incidence of CR-BFG isolated from our hospitalized patients has become an important problem. Therefore, we aimed to determine the frequency and associated factors for intestinal colonization by carbapenem-non-susceptible BFG (CNS-BFG) among adult patients hospitalized at intensive care units, neurosurgery and internal medicine wards in our hospital.

Methods: Rectal swabs (n = 1200), collected from 766 patients between February 2014 and March 2015, were inoculated onto kanamycin-vancomycin-leaked blood agar containing 0.125 mg/L meropenem. The isolates were identified by MALDI-TOF MS. Susceptibility testing was performed by agar dilution method. The carbapenemase gene (*cfiA*) was detected by PCR. Logistic regression analysis was used to evaluate the associated factors for intestinal colonization by CNS-BFG.

Results: A total 180 non-duplicate BFG isolates were obtained from 164 patients.

Ten different species, including *Parabacteroides distasonis* (n = 46, 25.6%), and *Bacteroides fragilis* (n = 30; 16.6%), were identified. Twenty-five percent of the isolates were non-susceptible to meropenem (MIC >2 mg/L). The highest prevalence of meropenem resistant strains (MIC >8 mg/L) was detected among *B. fragilis* (n = 12), followed by *Parabacteroides* spp. (n = 4). All but one *B. fragilis* strains were *cfiA* gene positive. Hospital admission, increasing Charlson score, use of antibiotics; including carbapenems in past three months, colonization with other accompanying carbapenem-resistant Gram negative bacteria (*Enterobacteriaceae, Acinetobacter baumanni*i and *Pseudomonas aeruginosa*), and having undergone surgical operations were significantly associated with RCS- BFG colonization.

Conclusions: The high carriage rate of CNS-BFG in hospitalized patients may lead to worse clinical outcomes, such as serious infections and mortality, and deserves attention.

1. Introduction

Bacteroides fragilis group (BFG) bacteria, the gram-negative anaerobic bacilli, are part of the human resident microbiota. They can cause severe opportunistic infections, including intraabdominal infection and bloodstream infection. Bacteroides fragilis is the most frequently isolated pathogen followed by B. thetaiotaomicron, B. vulgatus, B. ovatus and Parabacteroides distasonis. Moreover, BFG isolates are of great importance as highly resistant pathogens to antimicrobials used in treatment of anaerobic infections [1].

BFG has the ability to develop resistance mechanisms to almost all antimicrobials. The carbapenem-resistant BFG (CR-BFG) strains have

Abbreviations: Carbapenem-resistant Bacteroides fragilis group, CR-BFG; Carbapenem-non-susceptible Bacteroides fragilis group, CNS-BFG.

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been reported in several countries recently with increasing global attention. The most common way that *Bacteroides* become resistant to carbapenems is by producing carbapenemase, a metallo-β-lactamase enzyme encoded by *cfi*A gene. Furthermore, carbapenem resistant *Bacteroides* are also resistant to other β-lactams and β-lactamase inhibitor combinations. Most of CR-BFG isolates also display combination of multi-drug resistance to other important antibiotic classes, resulting in limited therapy options [2]. Infections due to CR-BFG may lead to undesired outcomes, especially in vulnerable patients with comorbidities [1].

Carriage of CR-BFG in the gastrointestinal tract may precede and possibly serve as a source for subsequent clinical infection at high-risk units such as intensive care, haematology/oncology, transplant, renal haemodialysis, and gastroenterology/gastrointestinal surgery units. Gut colonization of multi-drug resistant gram negative bacteria inpatients was reported to be associated with an increased risk of developing an infection, and death [3]. In this context, identifying predictor factors for development of infections due to CR-BFG in patients initially colonized with CR-BFG isolates is important for better management of such infections.

Active surveillance for carriage of carbapenem-resistant Gram negative bacteria (CR-GNB), declared as urgent threat pathogens for health-care system by Centers for Disease Control and Prevention (CDC), has become an integral part of local and national programs in the healthcare setting [4]. Although phenotypic and molecular-based techniques for screening and identifying CR-GNB (*Enterobacteriaceae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*) are commercially available, this is not the case for anaerobes [5,6].

The aim of this study was to determine the intestinal carriage rate of carbapenem-non-susceptible BFG (CNS-BFG) in hospitalized adult patients and the frequency of the *cfi*A gene. Furthermore we tried to identify associated factors for CNS-BFG colonization among patients.

2. Material and methods

This study was executed at a university hospital, a tertiary care canter with 650 hospital-beds. The number of annual hospital admissions was 13,911 and inpatient days was 189.874 for the year 2014. There were 33 secondary and tertiary intensive care beds of adult patients.

A case-control study was conducted, comparing reduced carbapenem susceptible-BFG (RCS-BFG) colonized patients with non-colonized patients at a ratio of 1:1.5 as they were matched on sex and age (±1 year). The controls were randomly selected among patients who stayed on the same ward/at the same time [7].

2.1. Patients and specimen collection

The study was carried out concurrently with the infection control program obtaining rectal surveillance cultures to screen for the presence of CR-GNB and vancomycin-resistant *Enterococcus* (VRE) colonization in adult patients in intensive care units (ICU), neurosurgery and internal medicine departments. Rectal swabs were obtained weekly from all hospitalized patients admitted to these wards between February 2014 and March 2015. Further screening was not performed on patients who had three consecutive negative samples, in accordance with the decision of the infection control committee. The study protocol was approved by the Ethics Committee of University Medical School (No. June 12, 2020.690).

Data related to the cases and controls, including demographic characteristics and possible associated factors, such as history of hospitalization, type and duration of antibiotic use, ICU stay, surgical history, underlying diseases, the Charlson comorbidity index (CCI) were obtained from the hospital records retrospectively.

2.2. Microbiological methods

To select RCS-BFG bacteria, we designed the KVLBA-CARBA agar. For preparation of this selective medium, we added 0.125 mg/L meropenem (ECOFF; the screening cut-off MIC values) to per liter of Brucella leaked blood agar with kanamycin (0.75 ml at 100 mg/ml stock solution) and vancomycin (1 ml at 7.5 mg/ml stock solution) which is used for isolation of BFG from clinical samples in our routine practice [8]. Each rectal swab was transferred into 5 ml Brucella broth to get suspension. An inoculum volume of 100 μL suspension was immediately transferred onto the KVLB-CARBA. After 48-h incubation period in an anaerobic chamber (Bactron-I, SHELLAB, USA), different colonies on the KVLBA-CARBA plates were subcultured for aerotolerence testing. All anaerobic colonies were submitted for identification using MALDI-TOF MS (Vitek MS, bioMérieux, France) automated system. One isolate belonging to the same BFG species was selected from each patient for testing. Antimicrobial susceptibility of isolates against meropenem was determined by agar dilution method, MIC>2 mg/L was accepted as meropenem non-susceptible, as well as MIC>8 as resistant [9,10]. The drugs; meropenem, kanamycin and vancomycin, and Brucella media used in this study were product of Sigma-Aldrich, (St.Louis, Missouri, USA).

2.3. DNA extraction and cfiA carbapenemase gene amplification

Bacterial DNA was extracted by heating. The *cfi*A gene was detected by polymerase chain reactions (PCR) using specific primers; GBI-1 F 5′-CCCAACTCTCGGACAAAGTG-3 and GBI-2 R 5′-AGTGAATCGGTGAATC-CATG-3 [2].

2.4. Statistical analysis

Univariate analyses were done by Mann Whitney U and Chi–square tests. All statistical tests were two-sided. For multivariate analysis, possible factors identified with univariate analyses ($p < 0.1$) were further entered into a logistic regression analysis to determine independent factors for the outcome. The R^2 (Nagelkerke) value was used to assess model fit. Analyses were performed using SPSS11.0 system software. Significance was set at $P < 0.05$ [7].

3. Results

3.1. Distribution of species and prevalence of meropenem resistance

A total of 1200 rectal swabs, collected consecutively from 766 adult patients were included for analysis. Of these patients, 164 (21.4%) were found to be colonized with any BFG isolates that have meropenem MIC values ≥ 0.25 mg/L. From colonized patients, a total of 180 non-duplicate BFG bacteria were processed. Altogether 10 different species, including *P. distasonis* (n = 46; 25.6%), *B. vulgatus* (n = 35; 19.4%), *B. ovatus* (n = 34; 18.8), *B. fragilis* (n = 30; 16.6%), were identified. According to EUCAST clinical breakpoints 13.9% and 11.1% of isolates were “susceptible, increased exposure (I)” and resistant (R) to meropenem, respectively. The highest prevalence of meropenem resistant strains was detected among *B. fragilis* (n = 12, 40%), followed by *Parabacteroides* spp. (n = 4, 8.3%). Non-susceptibility (“R” isolates and those with “I” taken together) rates for these isolates, were increased to 60% and 27%, respectively. See Table 1 for distribution of BFG isolates and those of MIC values by species level included in the study.

3.2. Prevalence of the cfiA gene in Bacteroides fragilis isolates

All *B. fragilis* isolates, except one, harboured the *cfi*A gene (Table 1).

3.3. Factors associated with RCS-BFG colonization

Patients colonized with RCS-BFG strains had higher mean Charlson Comorbidity Score (3.48 ± 2.57 vs 2.63 ± 1.90, $p < 0.01$) when compared to control group. Use of any antibiotics in past three months was higher (72.6% vs 58.8%) in RCS-BFG colonized patients. Total

Table 1
Distribution of *Bacteroides fragilis* group isolates and the meropenem MIC values.

Presence of *cfi*A gene	BFG species	*Meropenem MIC value; mg/L**									*Total n:*
		S				I	R				
		0.25	0.5	1	2	4	8	16	32	64	
cfiA gene positive	*B. fragilis*			6	5	**3**	3	1	1	10	29
cfiA gene negative	*B. fragilis*			1							1
	B. ovatus	1	11	9	10	**2**	1				34
	B. theatoitomicron	1	6	8	2	**1**	1				19
	B. uniformis		2	1	4	**1**		1			9
	B. vulgatus	1	15	10	4	**2**	1			2	35
	Bacteroides spp.**	2	1				1			1	5
	Parabacteroides spp.***	4	13	14	4	**6**	3	1	1	2	48
Total n:		9	48	49	29	**15**	10	3	2	15	180

*S; susceptible, I; increased exposure R; resistant, ***Bacteroides* spp.*; B. caccae, B. eggerthi, B.stercoris, ****Parabacteroides* spp.*; P. distasonis, P. goldsteinii.*

treatment days of antibiotics in patients with colonized by RCS-BFG bacteria were higher than those among control group (mean 11.9 ± 7.5 vs 3.4 ± 6.6, $p < 0.01$). Co-colonization with CR-GNB was significantly higher in RCS-BFG colonized patients (7.9% vs 4.5%, $p < 0.01$). Co-colonization with VRE was similary between two groups. Proportion of patients with history of previous hospital admission and any surgical procedure in the last three months was significantly higher in patients colonized with RCS-BFG (Table 2).

4. Discussion

There are a variety of national and international guidelines on screening for carriage of CR-GNs, declared as urgent threat pathogens for healthcare system by the CDC [4]. However, no consensus guideline on CR-BFG definitions exist to date. Due to the high carbapenem resistance rate in our clinical *B. fragilis* isolates, we wanted to know the intestinal carriage of RCS-BFG isolates in our hospitalized patients. In this context we designed a definition method to detect the RCS-BFG colonization based on international expert proposals on the screening of other CR-GNs [4,5].

BFG bacteria, inhabitants of the gut, can cause infection in many parts of the body. Spread of strains among patients is not known, although a few studies have been conducted on this topic. Niestępski et al. [11] isolated multi-drug resistant BFG isolates with a high variety of antibiotic resistance genes from hospital wastewater. Earlier studies based on genotyping and serotyping suggested that strains of *B. fragilis* might disseminate among patients [12,13]. Arpin et al. [14] reported a case of cross-infection due to an imipenem-resistant *B. fragilis* strain associated with a totally implantable venous port. According to these data, it can be speculated that BFG isolates may spread in hospitalized patients. Nevertheless, spread of the CR-BFG bacteria seems to be limited in the hospital environment, they are more probably causing endogenous infections. However, detection of CR-BFG carriage in the gastrointestinal tract may be important and should be performed for two reasons. First, it may serve as a source for subsequent clinical infection especially in patients with different comorbidities such as malignancy, immunosuppression. Second, CR-BFG bacteria are resistant to other antibiotics as well, hence they may cause therapeutic failure and a higher mortality rate.

Table 2
The risk factors for acquisition of colonization of reduced carbapenem susceptible *Bacteroides fragilis* group bacteria (RCS-BFG).

	Univariate analysis			Multivariable analysis	
Variable	RCS-BFG	Control	p-value	Odds Ratio	p-value
Male (%)	90 (54.9)	120 (54.3)	>0.05		
Age ≥ 60	80 (42.6)	109 (57.7)	>0.05		
Charlson's score, mean ± SD	3.48 ± 2.57	2.63 ± 1.90	<0.01	1.21	<0.01
Surgical history in previous 3 months	58 (35.4)	37 (16.7)	<0.01	3.86	<0.01
Presence of colonization of the CR-GNB* (%)	48 (29.3)	23 (10.4)	<0.01	–	–
Presence of colonization of the VRE** (%)	13 (7.9)	10 (4.5)	0.240	–	–
Admission to hospital in previous 3 monhts (%)	119 (72.8)	70 (31)	<0.01	2.25	<0.01
Ward of hospital stay, ICU***	116 (70.7)	130 (58.8)	<0.01	–	–
Total antibiotic days, mean ± SD	11.9 ± 17.5	3.4 ± 6.6	<0.01	–	–
Any antibiotic use in previous 3 months	119 (72.6)	70 (31.7)	<0.01	3.08	<0.01

*CR-GNB; Carbapenem-resistant Gram negative bacteria, **VRE; Vancomycin-resistant *Enterococcus,* ***ICU; Intensive care units.

Studies on the prevalence of antimicrobial susceptibility of BFG bacteria in faecal microbiota are rare, moreover, most of them have been performed on healthy adults. Hansen et al. [15] published a study on investigation of acquisition of antimicrobial resistance in the BFG in faecal samples from hospitalized patients receiving broad-spectrum antibiotics. In comparison, this study was similar to our study, but it was different in various aspects, such as the patient population involved and the samples. While they tested faecal samples of patients treated at the departments of haematology, oncology and infectious diseases, we processed rectal swabs from patients in intensive care units, neurosurgery and internal medicine departments. We both used the KVBL medium to isolate BFG bacteria, but we added meropenem (0.125 mg/L) to make a more selective medium for screening the RCS-BFG isolates, based on the ECOFF value recommended for BFG [8]. The distribution of species differs across these two studies too. While they found *B. ovatus/xylanisolvens* strains as the dominant species, we mostly isolated *Parabacteroides* spp. and *B. vulgatus* The use of media with different selective properties in these two studies for BFG isolation most likely affected the results; hence a clear conclusion could not be drawn for comparisons with isolates about carbapenem resistance values.

In the present study, the high rate of CNS-BFG bacterial colonization in the hospitalized patients was consistent with the results of our previous studies with clinical isolates. Since the isolation of the first imipenem-resistant *B. fragilis* at our hospital in a thirty-year period, the incidence of such resistance has increased up to 10%, which was higher than those reported from the other countries [3,16,17]. The reason was probably the increased usage of carbapenems in severely ill patients. Significant resistance to carbapenems has developed not only in *B. fragilis* isolates but also in other clinical Gram negative aerobic bacteria [18].

Except one, all *B. fragilis* isolates harboured the *cfiA* gene. Considering our previous studies, the high prevalence of *cfi*A was not a surprise [16]. The *cfi*A-positive isolates rate (27%) was substantially higher than those

reported in other countries, ranging from 4.1 to 9.4% [1,3,17]. Not all *B. fragilis* isolates carrying the *cfi*A gene are resistant to carbapenems. However, they have high potential to be resistant, if the *cfiA* gene be expressed by an insertion sequence (IS) element, a mobile DNA capable of displacement on the same bacterial chromosome or be transferred from one bacterium to another [2]. Our findings reveal another important issue, the resistance to carbapenem in non-fragilis *Bacteroides isolates*. As none of the studies describing *cfiA* gene as an expressing carbapenemase production in non-fragilis BFG, carbapenem resistance in these bacteria were most probably due to porin mutations or the overexpression of efflux pumps especially in combination with the hyper production of β-lactamase enzymes [1–3]. In this regard, carbapenem resistance in BFG, which may be mediated by carbapenemase enzymes or other mechanisms, appears to be a threat, accordingly it is necessary to closely monitor their clinical importance.

The current study shows a significant association ($p < 0.05$) between previous exposure to various group antibiotics and intestinal colonization with RCS-BFG bacteria. In a Europe-wide antibiotic resistance survey, the absence of resistance to imipenem among BFG isolates recovered from intestinal microbiota of healthy people shows the importance of previous non-exposure to carbapenems [19]. Similarly, Hansen et al. [15] reported that carbapenem therapy significantly increased the number of carbapenem resistant BFG strains in the faeces of patient.

Exposure to antibiotics, including penicillins, cephalosporins, carbapenems, and fluoroquinolones, was reported to be associated with increased risk of CR-GNs colonization among hospitalized patients. Furthermore, gut colonization of multidrug-resistant Gram-negative bacteria was reported to increase the risk of developing infections and death [3]. In present study, the associated factors for RCS-BFG acquisition were documented for CR-GNs colonization. We think that this is due to the similar risk factors and patient characteristics in the formation of both RCS-BFG and CR-GNs colonization.

Another important issue that should be emphasized in this study was the presence of accompanying intestinal colonization of CR-GNs with RCS-BFG. It should be considered that BFG isolates are intrinsically resistant to the antimicrobials used in the treatment of CR-GNs, such as colistin [1]. If colistin, which is used as a last-resort treatment, is given without considering this condition, treatment failure may occur for mixed infection caused by CR-GNs and RCS-BFG.

This study also has some limitations; there are currently very few tests available for screening carbapenem resistant BFG. Bacteroides chromogenic agar (BCA), recently designed, allowed *B. fragilis* to differ from other BFG members through its effective inhibition of other bacteria as well as forming black colonies, to differ from other members of BFG [20]. In this study, we designed a selective medium, KVLBA-CARBA, which did not create any colour difference in colonies. Differentiation of BFG should have been more obvious on BCA, than KVBL-CARBA. For identification, while selecting different colonies according to colony morphology, we may have missed some species and this might be the first limitation of our study. Second; we performed a case control study to identify associated factors for colonization. However, we did not monitor the patients and the control group for the occurrence of anaerobic infections due to RCS-BFG bacteria. This does not allow us to evaluate how RCS-BFG bacteria are potentially pathogenic for hospitalized patients. Third, the screening of RCS-BFG bacteria rely on laborious and time-consuming assays. It is not a test that can be performed in laboratories without anaerobic culture practice. Despite these limitations, we believe that further screening tests for RCS-BFG isolates in the faecal microbiota of healthy or diseased people will be useful in understanding future potential hazards.

5. Conclusions

In this study, high rate of RCS-BFG bacterial colonization was determined inpatients. Moreover, the presence of other accompanying CR-GN bacteria colonization was significantly higher. Additionally, underlying chronic diseases, use of carbapenems and other antimicrobials were the associated factors for RCS-BFG bacterial colonization, which underscores the importance of antibiotic stewardship programs. Consequently, the colonization of RCS-BFG isolates may lead to undesirable outcome, such as serious infections and mortality and deserves significant attention.

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CRediT authorship contribution statement

Nurver Ulger Toprak: All authors meet the ICMJE authorship criteria. , All authors have seen and approved the manuscript, and contributed significantly to the work, Formal analysis, The statistical analysis of data were performed. **Oncu Akgul:** All authors meet the ICMJE authorship criteria. . **Huseyin Bilgin:** All authors meet the ICMJE authorship criteria. , were responsible for the study design and its conduct. Data collection and experimentel study were performed by O. Akgul, G. Altinkanat Gelmez and E. Sayin. **Ayse Nilufer Ozaydin:** All authors meet the ICMJE authorship criteria. , Formal analysis, The statistical analysis of data were performed. **Gulsen Altinkanat Gelmez:** All authors meet the ICMJE authorship criteria. . **Elvan Sayin:** All authors meet the ICMJE authorship criteria. . **Uluhan Sili:** All authors meet the ICMJE authorship criteria. , Formal analysis, contributed to data analysis, manuscript drafting and revision, and also supervised the study. **Volkan Korten:** All authors meet the ICMJE authorship criteria. , Formal analysis, contributed to data analysis, manuscript drafting and revision, and also supervised the study. **Guner Soyletir:** All authors meet the ICMJE authorship criteria. , Formal analysis, contributed to data analysis, manuscript drafting and revision, and also supervised the study.

Declaration of competing interest

No conflict of interest was declared by the authors.

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