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Original Article

Anaerobic bloodstream infections in Italy (ITANAEROBY): A 5-year retrospective nationwide survey

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ABSTRACT

Introduction: A lack of updated data on the burden and profile of anaerobic bloodstream infections (ABIs) exists. We assessed the incidence of ABIs and trends in antimicrobial resistance in anaerobes isolated from blood in Italy.

Material and methods: We conducted a retrospective study on 17 Italian hospitals (2016–2020). Anaerobes isolated from blood culture and their *in vitro* susceptibility profiles (EUCAST-interpreted) were registered and analyzed.

Results: A total of 1960 ABIs were identified. The mean age of ABIs patients was 68.6 ± 18.5 years, 57.6% were males. The overall incidence rate of ABIs was 1.01 per 10.000 patient-days. Forty-seven% of ABIs occurred in medical wards, 17% in ICUs, 14% in surgical wards, 7% in hemato-oncology, 14% in outpatients. The three most common anti-anaerobic tested drugs were metronidazole (92%), clindamycin (89%) and amoxicillin/clavulanate (83%). The three most common isolated anaerobes were *Bacteroides fragilis* (n = 529), *Cutibacterium acnes* (n = 262) and *Clostridium perfringens* (n = 134). The lowest resistance rate (1.5%) was to carbapenems, whereas the highest rate (51%) was to penicillin. Clindamycin resistance was >20% for *Bacteroides* spp., *Prevotella* spp. and *Clostridium* spp. Metronidazole resistance was 9.2% after excluding *C. acnes* and *Actinomyces* spp. *Bacteroides* spp. showed an increased prevalence of clindamycin resistance through the study period: 19% in 2016, 33% in 2020 ($p \leq 0.001$).

Conclusions: Our data provide a comprehensive overview of the epidemiology of ABIs in Italy, filling a gap that has existed since 1995. Caution is needed when clindamycin is used as empirical anti-anaerobic drug.

1. Introduction

Anaerobes are responsible for 1–17% of bloodstream infections, with some studies reporting percentages as high as 30% [1–4]. This heterogeneity depends on the study period, the country and the setting of the evaluation and the isolation or identification methods. In anaerobic bloodstream infections (ABIs), *Bacteroides fragilis* is reported to be the most frequently isolated strain, followed by *Clostridium* spp., *Fusobacterium* spp. and *Peptostreptococcus* spp [5,6]. ABIs most frequently are secondary to infections of intra-abdominal organs, soft tissues, biliary or urinary tract as well as to surgical interventions including dental procedures and oncological conditions [7–12]. ABIs entail prolonged hospitalization and are associated with high mortality rates. While waiting for susceptibility testing, empirical therapy can make a difference in the clinical and microbiological outcome, although different authors have reported discordant results [6,9,13]. Nevertheless, guidelines on the treatment of ABIs are lacking and few studies have been performed in recent years. In the worrisome scenario of alarming antimicrobial resistance rates, updated epidemiological studies evaluating trends in incidence and antimicrobial resistance may change the currently prescribed treatments and/or current antimicrobial stewardship strategies.

The last Italian nationwide survey [5] evaluated ABIs from 14 Italian hospitals (located in 9 out of 20 Italian regions) in the study period July 1991 to June 1992. A total of 255 ABIs were included in the survey, highlighting a slight predominance of Gram-negative anaerobes over Gram-positive anaerobes (52% vs 48%) and a much greater incidence of ABIs in medical wards than in surgical wards (73% vs 27%). Evaluation of antimicrobial resistance rates was not performed.

In order to provide updated data on incidence and susceptibilities, we performed a retrospective nationwide survey to evaluate incidence of ABIs and trends in antimicrobial resistance in anaerobes isolated from blood cultures in Italy.

2. Methods

We performed a multicentric retrospective observational study including all consecutive anaerobes isolated from blood culture from 17 participating Italian hospitals (located in 11 out of 20 Italian regions) collected from January 2016 to December 2020 (Table S1, Fig. S1). The primary aim of the present investigation was to assess the overall ABIs prevalence and the trend in ABI incidence rate over the study period. Moreover, the prevalence of antimicrobial resistance to anti-anaerobic drugs and its modification over time was explored as a secondary objective. An ABI episode was defined as the isolation of an anaerobic bacterium from blood cultures. Subsequent isolation of the same organism for the same patient was considered as a novel ABI episode only if isolated at least 30 days after the last previous positive blood culture for the same organism [14].

Inclusion criteria were established as: admission in one of the participating hospitals in the period of study, positive ABI in the period of study.

For patients meeting the inclusion criteria, we recorded the following data: age, gender, nationality, clinical setting in which the pathogen was isolated (medical or surgical wards, intensive care units, oncology or haematology wards, and outpatient settings) and susceptibility testing results. We also collected general information from each hospital: species identification method, antimicrobial susceptibility method, number of hospital beds (see Supplemental Table 1). In brief, isolation of anaerobic bacteria was mostly performed using Schaedler agar in anaerobic conditions (mostly using hermetic container with sachets as gas generators for anaerobic conditions; i.e. Genbag Anaerobic, Biomeriéux, Mercy l'Etoile, France; AnaeroGen, Thermo Fisher, Waltham, MA, US). Bacterial identification methods were: Vitek2 (Biomeriéux, Mercy l'Etoile, France), for biochemical identification, Vitek MS (Biomeriéux) and Bruker Biotyper (Bruker Daltonics Inc., Raleigh, NC, USA), for MALDI-TOF mass spectrometry-based identification. Susceptibility

testing methods were: broth microdilution commercial systems (Sensititre Anaerobe MIC Plate, Thermo Fisher, Waltham, MA, USA; Merlin GmbH, Germany; ATB ANA, Biomeriéux) and gradient test (Etest, Biomeriéux; MIC Strip, Liofilchem srl, Roseto degli Abruzzi, Italy). In particular, gradient tests were used by 15 centers, while four centers used broth microdilution systems (two centers used both systems, but in different periods). Results of antimicrobial susceptibility testing were interpreted by each Hospital according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (www.eucast.org).

Peptostreptococcus spp., *Peptoniphilus* spp., *Anaerococcus* spp., *Finegoldia magna* and *Parvimonas* spp. were included in a single Gram-positive anaerobic cocci group (GPAC).

Susceptibility data were available for: penicillin, amoxicillin/clavulanate, ertapenem, imipenem, meropenem, clindamycin, vancomycin, metronidazole and chloramphenicol. Anaerobes with less than five observations over a certain year were excluded from the analyses, Since *Actinomyces* spp. and *Cutibacterium acnes* are intrinsically resistant to metronidazole, they were not considered in susceptibility analyses. Statistical analysis was performed to evaluate both the trends in incidence rate of ABIs and the trends in prevalence of antimicrobial resistance over the study period. The incidence rate of ABIs was calculated as the number of episodes per 10,000 patient days. The changes in the incidence rate of ABIs over the study period were assessed through generalized linear mixed models based on Poisson regression or negative binomial regression, in the case of absence vs. presence of overdispersion in count data, respectively. Time in trimesters was the independent variable in all models, and the center was included as a random effect. The prevalence of antimicrobial resistance was calculated as the number of resistant isolates divided by the total number of tested isolates. The difference in resistance rate to different antimicrobial agents over the study years was tested through linear-by-linear association test for trend in proportions. The analyses were performed using R Statistical Software 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

The study was approved (n° 112_2020) by the Ethics Committee of the coordinator center (Azienda Sanitaria Universitaria Giuliano Isontina ASUGI, Trieste, Italy), in agreement with the Declaration of Helsinki (1964) and its later amendments.

3. Results

During the study period, a total of 215,665 positive blood cultures were considered, among which 3477 (1.6%) detected the presence of anaerobe bacteria. After excluding repetitive isolates within a 30-days period, a total of 1960 ABIs were included in the study. The mean age of patients with ABIs was 68.6 ± 18.5 years, 1128 (57.6%) of them were males. The overall incidence rate of ABIs was 1.01 per 10,000 patient-days (Fig. 1). The three most common anaerobes isolated from ABIs were *B. fragilis* (n = 529; 27.0%), *Cutibacterium acnes* (n = 262; 13.4%) and *C. perfringens* (n = 134; 6.8%). A total of 927 (47.3%) of ABIs occurred in medical wards, 331 (16.9%) in intensive care units, 280 (14.3%) in surgical wards and 141 (7.2%) in hemato-oncology facilities, while the remaining 281 (14.3%) occurred in outpatient settings. The most common anti-anaerobic tested antibiotic was metronidazole (n = 1819; 92.8%), followed by clindamycin (n = 1747; 89.1%), amoxicillin/clavulanate (n = 1631; 83.2%), imipenem (n = 1272; 64.9%), penicillin (n = 1227; 62.6%), meropenem (n = 1004; 51.2%), vancomycin (n = 576; 29.3%), chloramphenicol (n = 423; 21.6%), and ertapenem (n = 308; 15.7%).

The anti-anaerobic drugs with the lowest resistance rate were carbapenems (overall resistance rate: 1.5%), followed by chloramphenicol (4.7%), amoxicillin/clavulanate (5.1%), vancomycin 4.5%, metronidazole (9.2% after excluding *Actinomyces* spp. and *C. acnes*), clindamycin (22.4%), while penicillin (51.5%) showed the highest resistance rates (Fig. 2). No multidrug-resistant (MDR) isolate were detected in our survey, with MDR isolates defined as those with acquired non-susceptibility to at least one agent in three or more antimicrobial categories.

Detailed resistance of specific anaerobe groups to antimicrobials are shown in Fig. 3. Tables 1 and 2 describe the overall and bacteria-specific trend of resistance over the time-span considered by the present investigation.

The time trend analysis of the antibiotic susceptibility profiles showed that *Bacteroides* spp. had an increased clindamycin resistant prevalence over the study period, rising from 19% in 2016 to 34% in 2020, with a prevalence as high as 41% in 2019 ($p \leq 0.001$) (Table 2a).

4. Discussion

Infections caused by anaerobes are largely underestimated, mostly due to their fastidious nature that makes their isolation and identification in the laboratory routine difficult. In addition, not all laboratories perform antibiotic susceptibility testing for anaerobes. This is an important obstacle for an extensive knowledge of the

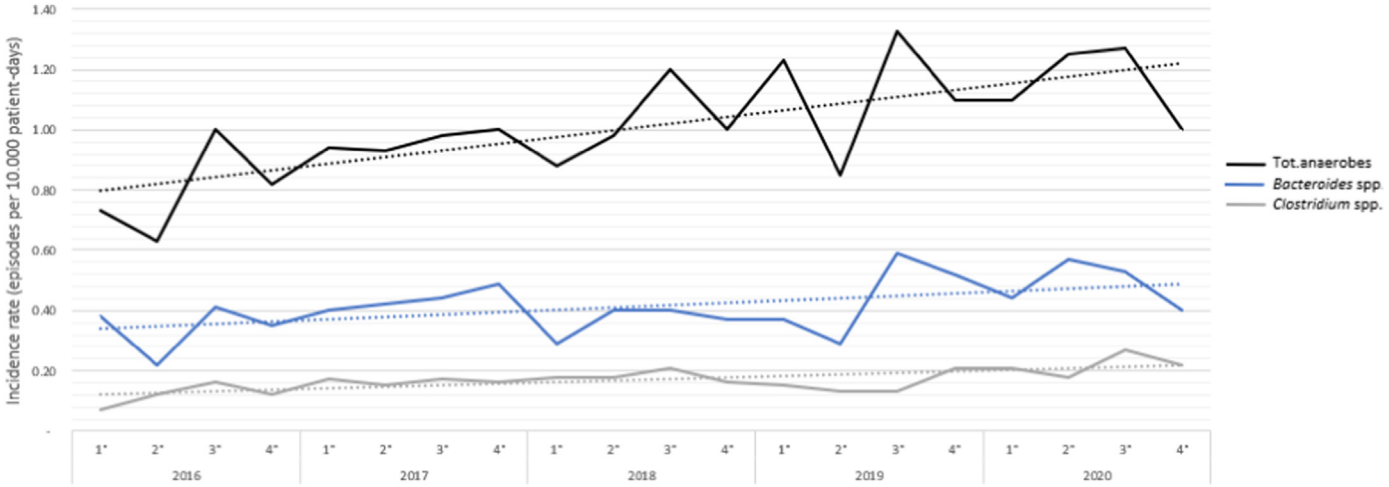

Fig. 1. Trends in the incidence of anaerobic bloodstream infections over 5 years across 17 Italian centers.

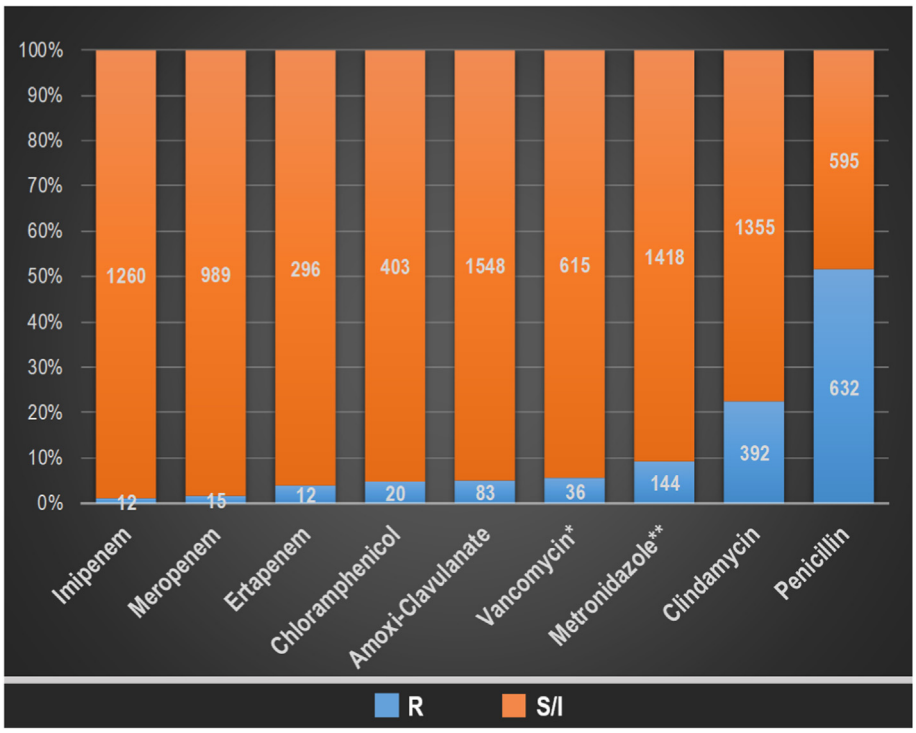

Fig. 2. Overall antibiotic resistance profiles.

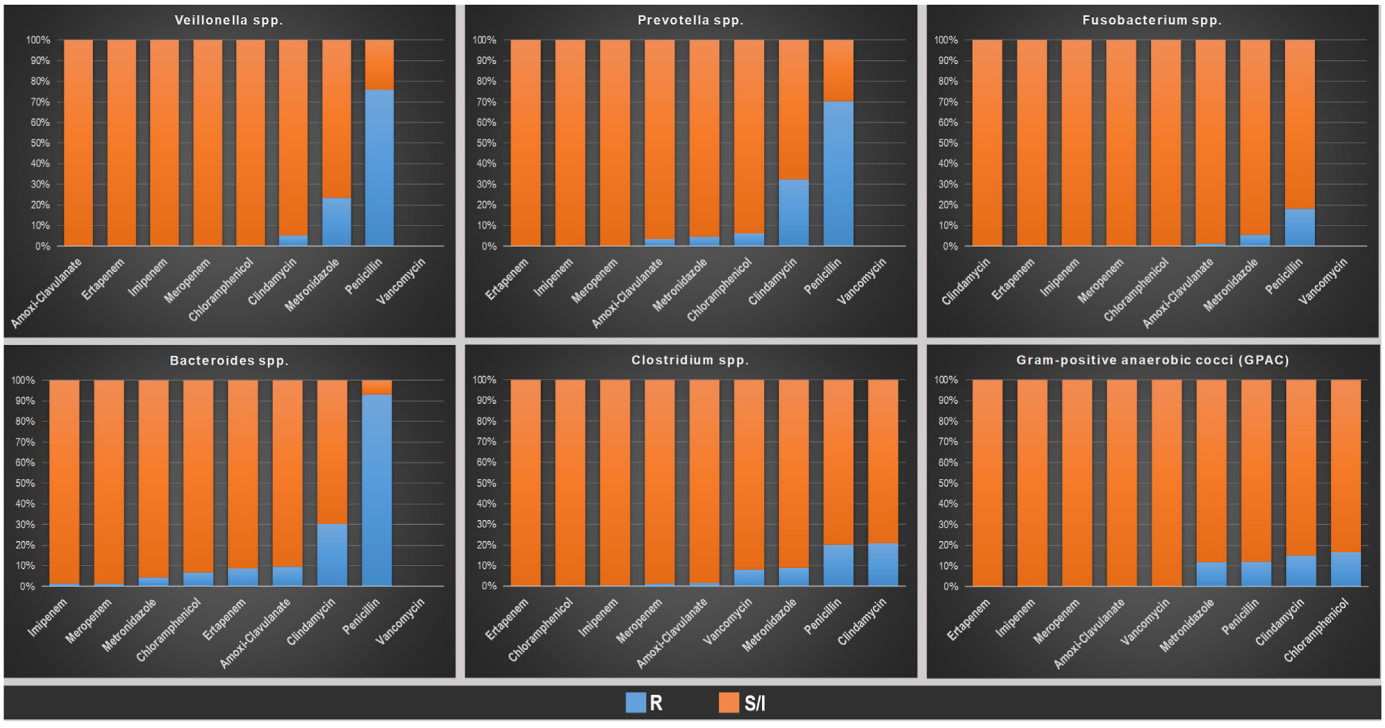

Fig. 3. Antibiotic resistance profiles according to anaerobic isolate.

incidence of anaerobic infections (especially ABIs) and of the diffusion of resistance traits, making it difficult to evaluate the real clinical impact and the related epidemiologic scenario. In this context, our data provides a new and broad overview on the epidemiology of ABIs in Italy, representing the largest Italian survey, filling a gap which has existed since 1995.

In the present investigation, the overall prevalence of ABIs was 1.6% of positive blood cultures, much lower than the previous Italian data (4%). This reduction could be possibly attributed to both medical and surgical patient care improvement. The overall

Table 1
Prevalence of resistance to different antimicrobial agents of **all study bacteria** isolates from ABI across 17 Italian centers over 5 years.

Antimicrobial agent	2016	2017	2018	2019	2020	*p*-value
Amoxicillin/Clavulanate	8/262 (3.1%)	25/327 (7.6%)	7/344 (2.0%)	22/381 (5.8%)	21/317 (6.6%)	0.224
Clindamycin	48/298 (16.1%)	80/362 (22.1%)	72/346 (20.8%)	107/397 (27.0%)	85/344 (24.7%)	**0.003**
Chloramphenicol	8/76 (10.5%)	2/108 (1.9%)	4/96 (4.2%)	4/83 (4.8%)	2/60 (3.3%)	0.202
Ertapenem	2/35 (5.7%)	2/59 (3.4%)	3/40 (7.5%)	3/100 (3.0%)	2/74 (2.7%)	0.423
Imipenem	3/216 (1.4%)	1/270 (0.4%)	2/274 (0.7%)	3/288 (1.0%)	3/224 (1.3%)	0.718
Meropenem	3/152 (2%)	2/192 (1.0%)	3/163 (1.8%)	5/262 (1.9%)	2/235 (0.9%)	0.637
Metronidazole*	21/259 (8.1%)	28/328 (8.5%)	34/317 (10.7%)	40/340 (11.8%)	21/318 (6.6%)	0.999
Penicillin	125/228 (54.8%)	148/267 (55.4%)	123/245 (50.2%)	122/261 (46.7%)	114/226 (50.4%)	0.077
Vancomycin	1/84 (1.2%)	6/109 (5.5%)	6/115 (5.2%)	11/156 (7.1%)	3/139 (2.2%)	0.776

ABI: anaerobic bloodstream infections. Bold *p*-values: statistically significant. *: after excluding *Actinomyces* spp. and *C. acnes*.

Table 2a
Prevalence of resistance to different antimicrobial agents of ***Bacteroides* spp.** isolates from ABI across 17 Italian centers over 5 years.

Antimicrobial agent	2016	2017	2018	2019	2020	*p*-value
Amoxicillin/Clavulanate	7/117 (6%)	21/171 (12.3%)	7/138 (5.1%)	15/169 (8.9%)	21/148 (14.2%)	0.139
Chloramphenicol	6/37 (16.2%)	2/63 (3.2%)	3/42 (7.1%)	3/51 (5.9%)	2/41 (4.9%)	0.198
Clindamycin	26/137 (19%)	53/187 (28.3%)	38/144 (26.4%)	76/184 (41.3%)	54/161 (33.5%)	**<0.001**
Ertapenem	2/16 (12.5%)	2/32 (6.3%)	3/19 (15.8%)	2/26 (7.7%)	2/32 (6.3%)	0.607
Imipenem	1/88 (1.1%)	1/127 (0.8%)	2/98 (2%)	1/104 (1%)	2/100 (2%)	0.5824
Meropenem	2/80 (2.5%)	1/111 (0.9%)	1/80 (1.3%)	2/121 (1.7%)	1/118 (0.8%)	0.556
Metronidazole	7/137 (5.1%)	9/188 (4.8%)	7/149 (4.7%)	9/185 (4.9%)	3/168 (1.8%)	0.191
Penicillin	86/93 (92.5%)	115/125 (92%)	89/96 (92.7%)	85/88 (96.6%)	91/98 (92.9%)	0.512

ABI: anaerobic bloodstream infections. Bold *p*-values: statistically significant.

Table 2b
Prevalence of resistance to different antimicrobial agents of ***Veillonella* spp.** isolates from ABI across 17 Italian centers over 5 years.

Antimicrobial agent	2016	2017	2018	2019	2020	*p*-value
Amoxicillin/Clavulanate	0/7 (0.0%)	n.d.	0/9 (0.0%)	0/8 (0.0%)	n.d.	/
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	/
Clindamycin	0/8 (0.0%)	1/5 (20.0%)	1/9 (11.1%)	0/10 (0.0%)	0/5 (0.0%)	0.614
Ertapenem	n.d.	n.d.	n.d.	n.d.	n.d.	/
Imipenem	0/5 (0.0%)	n.d.	0/7 (0.0%)	n.d.	n.d.	/
Meropenem	n.d.	n.d.	n.d.	0/6 (0.0%)	n.d.	/
Metronidazole	2/7 (28.6%)	0/5 (0.0%)	3/9 (33.3%)	3/9 (33.3%)	n.d.	0.872
Penicillin	7/7 (100%)	1/3 (33.3%)	4/7 (57.1%)	5/6 (83.3%)	2/2 (100%)	0.812

ABI: anaerobic bloodstream infections. n.d.: no data (no resistant isolates or less than five observations over the year).

incidence of ABIs was 1.01 per 10,000 patient-days. A slight trend toward an increase in ABIs through the years was observed, especially for *Bacteroides* and *Clostridium* spp.

A relevant strength of our survey is having described resistance profiles and antibiotic resistance trends for anaerobes isolated from patients with ABIs, presenting data not previously reported from Italy. Although not extensively tested, carbapenems retained the highest anti-anaerobic activity. These molecules have historically retained an excellent activity against anaerobes [15]. However, among them, ertapenem usually have lower antimicrobial activity towards *Bacteroides* spp., particularly for the *B. fragilis* group, with usually higher MIC values. This aspect is well evidenced in EUCAST MIC distribution for *Bacteroides*, with no epidemiologic cut-off value assigned for ertapenem (www.eucast.org). In this context, imipenem and meropenem appear more reliable options against *Bacteroides* spp. In our survey, resistance to carbapenems was detected only in *Bacteroides* spp. Recent data from laboratories in Germany, Slovenia, Turkey and Hungary showed that Gram-negative anaerobic bacteria have a resistance to imipenem $\leq$2% [16]. On the other side, penicillin could no longer be considered an acceptable drug for the empirical therapy of ABIs since more than 50% of the tested isolates were resistant. In particular, this trait of resistance was notable especially for *Bacteroides, Veillonella* and *Prevotella* spp. (resistance >90%, >70% and >70%, respectively). It is of note that, while *Bacteroides* spp. represent the one of the major β-lactamase producers at intestinal level, *Veillonella* spp. and *Prevotella* spp. represent main sources of β-lactamases in the human oral cavity [17]. Therefore, given that the resistance is mainly mediated by β-lactamases, the addition of a β-lactamase inhibitor to a β-lactam (e.g. amoxicillin) can significantly reduce resistance rates. β-lactams/β-lactamase inhibitors combinations retain good activity against anaerobes and susceptibility of at least 90% has been reported in the United States [18], Europe [19,20] and Asian countries [21,22]. Our data were consistent with this assumption, having documented an overall resistance to amoxicillin/clavulanate of 5% (Table 1). In particular, the resistance rate ranged from 0% (for *Veillonella* spp. and GPAC to 9.5% related to *Bacteroides* spp., indicating in this genus the presence of β-lactamases that could overcome the inhibition of clavulanate. The other genera accounted for a resistance rate <4%.

Clindamycin has long been considered an excellent drug for not severe anaerobic infections, however, according to our results it should be used with caution as empirical therapy, especially if it is the only antibiotic with anaerobic coverage of the antibiotic regimen. In fact, not only the overall resistance to clindamycin reached 20% for *Bacteroides* spp. and *Clostridium* spp. and even exceeded 30% for *Prevotella* (Table 2c), but also a clear statistically significant increase in clindamycin resistance among *Bacteroides* spp. was documented, with a prevalence as high as 41% in 2019 (Table 2a). This is in line with existing literature. In their European

Table 2c
Prevalence of resistance to different antimicrobial agents of ***Prevotella* spp.** isolates from ABI across 17 Italian centers over 5 years.

Antimicrobial agent	2016	2017	2018	2019	2020	*p*-value
Amoxicillin/Clavulanate	1/14 (7.1%)	0/7 (0.0%)	0/15 (0.0%)	1/13 (7.7%)	0/9 (0.0%)	0.658
Chloramphenicol	1/4 (25.0%)	n.d.	0/6 (0.0%)	n.d.	n.d.	0.178
Clindamycin	7/18 (38.9%)	3/8 (37.5%)	4/18 (22.2%)	5/13 (38.5%)	3/11 (27.3%)	0.574
Ertapenem	n.d.	n.d.	n.d.	n.d.	n.d.	/
Imipenem	0/9 (0.0%)	n.d.	0/12 (0.0%)	0/9 (0.0%)	0/5 (0.0%)	/
Meropenem	0/12 (0.0%)	n.d.	0/7 (0.0%)	0/7 (0.0%)	0/8 (0.0%)	/
Metronidazole	1/18 (5.6%)	1/7 (14.3%)	1/17 (5.9%)	0/13 (0.0%)	0/11 (0.0%)	0.280
Penicillin	8/15 (53.3%)	4/6 (66.7%)	9/11 (81.8%)	6/7 (85.7%)	4/5 (80.0%)	0.082

ABI: anaerobic bloodstream infections. n.d.: no data (no resistant isolates or less than five observations over the year).

Table 2d
Prevalence of resistance to different antimicrobial agents of ***Fusobacterium* spp.** isolates from ABI across 17 Italian centers over 5 years.

Antimicrobial agent	2016	2017	2018	2019	2020	*p*-value
Amoxicillin/Clavulanate	0/20 (0.0%)	1/22 (4.5%)	0/17 (0.0%)	0/14 (0.0%)	0/10 (0.0%)	0.618
Chloramphenicol	n.d.	0/6 (0.0%)	n.d.	n.d.	n.d.	/
Clindamycin	0/23 (0.0%)	0/22 (0.0%)	0/17 (0.0%)	0/13 (0.0%)	0/12 (0.0%)	/
Ertapenem	n.d.	n.d.	n.d.	n.d.	n.d.	/
Imipenem	0/11 (0.0%)	0/13 (0.0%)	0/10 (0.0%)	0/7 (0.0%)	0/8 (0.0%)	/
Meropenem	0/12 (0.0%)	0/15 (0.0%)	0/5 (0.0%)	0/11 (0.0%)	0/8 (0.0%)	/
Metronidazole	2/23 (8.7%)	1/23 (4.3%)	1/17 (5.9%)	1/15 (6.7%)	0/14 (0.0%)	0.396
Penicillin	2/12 (16.7%)	3/16 (18.8%)	2/10 (20.0%)	1/5 (20.0%)	1/6 (16.7%)	0.950

ABI: anaerobic bloodstream infections. n.d.: no data (no resistant isolates or less than five observations over the year).

Table 2e
Prevalence of resistance to different antimicrobial agents of ***Clostridium* spp.** isolates from ABI across 17 Italian centers over 5 years.

Antimicrobial agent	2016	2017	2018	2019	2020	*p*-value
Amoxicillin/Clavulanate	0/43 (0.0%)	3/54 (5.6%)	0/71 (0.0%)	1/48 (2.1%)	0/66 (0.0%)	0.348
Chloramphenicol	0/13 (0.0%)	0/11 (0.0%)	1/13 (7.7%)	0/9 (0.0%)	0/12 (0.0%)	0.962
Clindamycin	8/47 (17.0%)	14/60 (23.3%)	15/68 (22.1%)	11/58 (19.0%)	15/71 (21.1%)	0.881
Ertapenem	0/6 (0.0%)	0/6 (0.0%)	0/8 (0.0%)	0/14 (0.0%)	0/17 (0.0%)	/
Imipenem	0/33 (0.0%)	0/43 (0.0%)	0/53 (0.0%)	0/34 (0.0%)	1/46 (2.2%)	0.161
Meropenem	0/21 (0.0%)	0/23 (0.0%)	2/35 (5.7%)	0/41 (0.0%)	0/51 (0.0%)	0.634
Metronidazole	2/48 (4.2%)	5/65 (7.7%)	7/73 (9.6%)	11/61 (18.0%)	4/78 (5.1%)	0.482
Penicillin	9/30 (30.0%)	8/35 (22.9%)	9/43 (20.9%)	4/34 (11.8%)	7/43 (16.3%)	0.087
Vancomycin	1/31 (3.2%)	2/42 (4.8%)	5/44 (11.4%)	7/42 (16.7%)	3/64 (4.7%)	0.523

ABI: anaerobic bloodstream infections.

Table 2f
Prevalence of resistance to different antimicrobial agents of **Gram-positive anaerobic cocci (GPAC**, including isolates identified as *Peptostreptococcus* spp., *P. asaccharolyticus*, *P. anaerobius*, *Parvimonas* spp. *Anaerococcus prevotii*, *Finegoldia* spp., *Parvimonas micra*, *Peptoniphilus* spp.) from ABI across 17 Italian centers over 5 years.

Antimicrobial agent	2016	2017	2018	2019	2020	p-value
Amoxicillin/Clavulanate	0/9 (0%)	0/11 (0%)	0/7 (0%)	0/8 (0%)	0/14 (0%)	/
Chloramphenicol	n.d.	n.d.	n.d.	n.d.	n.d.	/
Clindamycin	2/10 (20.0%)	0/12 (0%)	1/8 (12.5%)	1/8 (12.5%)	4/15 (26.7%)	0.300
Ertapenem	n.d.	n.d.	n.d.	n.d.	n.d.	/
Imipenem	0/9 (0%)	0/9 (0%)	0/7 (0%)	0/6 (0%)	n.d.	/
Meropenem	0/6 (0%)	0/6 (0%)	n.d.	n.d.	0/8 (0%)	/
Metronidazole	1/10 (10.0%)	0/11 (0%)	1/8 (12.5%)	1/7 (14.3%)	3/15 (20.0%)	0.223
Penicillin	1/9 (11.1%)	0/5 (0%)	0/3 (0%)	2/5 (40%)	0/3 (0%)	0.548
Vancomycin	n.d.	n.d.	n.d.	0/6 (0%)	0/11 (0%)	/

ABI: anaerobic bloodstream infections. n.d.: no data (no resistant isolates or less than five observations over the year).

surveillance, Rodloff et al. reported a clindamycin resistance between 28 and 48% for Gram-negative anaerobes and from 11 to 22% for Gram-positive anaerobes [23]. These percentages are even higher in subsequent studies, which reported a resistance rate of 42% (Belgium) and over 50% (Spain) [15,24]. Thus, clindamycin resistance is spreading globally to the point where it is no longer recommended as first-line treatment for severe infections [25]. Regarding other genera in our survey, resistance to clindamycin reached 15% among GPAC, while it was 0% and 5% for *Fusobacterium* spp. and *Veillonella* spp., respectively.

Concerning the anaerobic species, *B. fragilis* is of great relevance for ABIs, being the most prevalent etiologic agent and showing the most important resistance traits, especially toward penicillin and clindamycin. Moreover, resistance to carbapenems in *Bacteroides* spp., even though sporadic, is a serious cause of concern. This resistance trait, mostly encoded by *cfiA* metallo β-lactamase gene in *Bacteroides fragilis*, is an emerging cause of concern, being already reported in this species worldwide [17,26–32]. It is of note that in

the last version of "EUCAST intrinsic resistance and unusual phenotypes" (document v3.3, 2021) resistance to carbapenems is not anymore considered an "unusual phenotype" for *Bacteroides* spp. Literature data indicate that this species exhibits the greatest arsenal of mechanisms for antibiotic resistance and displays the highest antibiotic resistance rates among anaerobes with an associated mortality rate of >19% [33].

Overall, metronidazole remains a reasonable option with a resistance rate of 9.2% (after exclusion of species with intrinsically reduced resistance, as *C. acnes* and *Actinomyces*); the only relevant exception was resistance rates detected in *Veillonella* isolates (24%), in the face, however, of a very small number of examined tests. This resistance trait has already been reported for *Veillonella* spp. isolates [17,34], but literature data are very scarce and further studies are needed to elucidate antibiotic resistance pattern in this species. Resistance rates for GPAC (11.8%) and *Clostridium* spp. (8.9%) were also notable, while *Bacteroides* spp., *Fusobacterium* spp. and *Prevotella* spp. accounted for resistance rates ≤5%. In general, the metronidazole resistance rate reported is high. No significant increase in metronidazole consumption has been reported in the last years from Italy, hence we can speculate that the increasing trend of resistance to this antibiotic among anaerobes could be attributable to a changing epidemiology. In particular, for 14 out of 17 participating centers the resistance rate for metronidazole ranged from 0% to 6%, while for the remaining three centers it ranged from 12% to 15% (average 5%). Historical cumulative data on metronidazole resistance does not exist for Italy, so a comparison is impossible.

Metronidazole resistance among *Bacteroides* and *Prevotella* spp. is now less than 2% in Europe and the United States [23,35]. Despite this, the number of isolates with lower metronidazole susceptibility has dramatically increased in Europe [19]. Interestingly, in their investigation, Sheikh et al. found increased metronidazole resistance in anaerobe bloodstream isolates when comparing bacteraemic vs non-bacteraemic isolates [36]. Highest resistance rates for metronidazole (from 3% to > 20%), among different anaerobic species (i.e. *Bacteroides* spp., *Clostridium* spp., *Fusobacterium* spp., *Peptostreptococcus* spp., *Prevotella* spp., *Veillonella* spp.) were reported from Asian countries [37–39]. The high metronidazole resistance rate found in *Veillonella* spp. strains approaches epidemiology found in some Asian countries where it reached even 27% [21]. Our data support the antimicrobial stewardship rule that metronidazole is redundant if the antibiotic regimen includes a carbapenem [40].

Vancomycin retained an overall good antimicrobial activity against Gram-positive anaerobes (4.5% of resistant strains), with a higher rate (8%) in the case of *Clostridium* spp. In this case, the presence of species intrinsically resistant to vancomycin (e.g. *C. ramosum* or *C. innocuum*), inside to *Clostridium* genus, but not identified at species level, could have increased the resistance rate to this antibiotic. Conversely, *C. perfringens* retained a lower rate of vancomycin resistance (2.2%), highlighting a marked difference with other clostridia. It is worth to highlight this, since *C. perfringens* is the most represented and clinically significant species among *Clostridium* spp. In our study *C. acnes* represented the second most prevalent microorganism isolated from blood cultures. *C. acnes* is a member of normal skin microbiota that can contribute to development of diseases such as acne vulgaris and prosthetic joint infections, but it was seldom associated with ABIs, being mostly considered a contaminant of positive blood cultures [41]. This represents a limitation of our study, because the real impact of *C. acnes* as a causative agent of ABIs was much lower if compared with other species here described (even if less represented).

Although tested in less than one quarter of the isolates (423), chloramphenicol displayed a good susceptibility profile, with a resistance rate of <5%. Susceptibility to chloramphenicol was mostly investigated among the *Bacteroides* spp. and clostridia. However, the resistance rate was almost totally attributed to *Bacteroides* spp., accounting for 6.8% of resistant isolates among this genus. Considering other genera, only two isolates were resistant to chloramphenicol, belonging to *Prevotella* spp. and *Clostridium* spp., respectively. This drug, almost abandoned in western countries, is currently being reconsidered for infections caused by MDR Gram-positive bacteria (e.g. vancomycin resistant enterococci) [42].

Our study has some limitation since the participating hospitals adopted different bacterial identification and susceptibility testing methods. In particular, only two centers used the Vitek2 system as bacterial identification method, while other three centers used this system partially, especially in the first period. This could provide a less reliable identification at species level for these centers. It is of note that systems based on mass spectrometry provide a more reliable identification than biochemical techniques, also considering their bigger database, now representing the gold standard for bacterial identification (including anaerobes). These limitations should be considered when interpreting the results.

Susceptibility of anaerobes to antibiotics has drastically changed during the last decades, going from profiles of complete susceptibility to multidrug resistance [15]. Given the unpredictable nature of antibiotic susceptibility of anaerobes, to perform antibiotic susceptibility tests is of utmost importance. We hope our data could be helpful for Italian and European clinicians, especially for guiding empirical therapies when anaerobes should be covered (e.g. intra-abdominal infections).

Conflicts of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.anaerobe.2022.102583.

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