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1 **Is the term “anti-anaerobic” still relevant?**

2

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24 For decades, the term “anti-anaerobic” has been commonly used to refer to antibiotics
25 exhibiting activity against anaerobic bacteria, also designated as anaerobes. This term is
26 used in various situations ranging from infections associated with well-identified pathogens
27 like *Clostridioides difficile* infections or *Fusobacterium necrophorum* in the Lemierre’s
28 syndrome that require specific antibiotic treatments, to polymicrobial infections generally
29 resulting from the decreased permeability of anatomical barriers (intestinal translocation,
30 stercoral peritonitis...) or infectious secondary localizations (brain abscess, infectious
31 pleurisy...). In these cases, the causal bacteria remain generally unidentified and the
32 antimicrobial treatment is empirical. However, the major progresses made since ten years in
33 the knowledge of human bacterial microbiotas have shown how diverse are the species
34 involved in these communities. Here, we sought to reappraise the concept of anti-anaerobic
35 spectrum in the light of the recent advancement in the microbiota field. We first highlight that
36 the term anaerobic itself does not represent the tremendous diversity of the bacteria it spans,
37 and then we stress that the antibiotic susceptibility profiles of anaerobic bacteria remains
38 unaddressed for most of them. Furthermore, we provide examples challenging the relevance
39 of the “antianaerobic” spectrum from a clinical and ecological perspective.

40

41 **Anaerobic bacteria: a single denomination for a wide spectrum of bacterial species**

42 For clinical microbiologists and infectious diseases physicians, the term “anaerobic bacteria”
43 stands as a broad denomination including species which commonality relates to their non-
44 tolerance to oxygen. While substantial efforts have recently been undertaken in the research
45 setting to cultivate intestinal anaerobes through various approaches(Zou et al., 2019), most
46 of them are not routinely culturable in clinical laboratories and remain poorly described. In
47 this regard, the development of extensive culture-based methods (also referred to as
48 culturomics(Lagier et al., 2016)) and culture-independent next-generation sequencing and
49 metagenomics has significantly contributed to better understand the anaerobic bacteria(Li et

50 al., 2014). All of these approaches have made it possible to describe better than ever the
51 human intestinal microbiota which is made of about 1,000 different species belonging to at
52 least seven different phyla, among which the Firmicutes and Bacteroidetes dominate, with an
53 estimated 10^{11} bacterial cells per gram of faeces. Thus, clustering such diverse species
54 under the generic “anaerobic bacteria” denomination only because of their non-tolerance to
55 oxygen appears simplistic.

56

57 **The antibiotic susceptibility pattern of most anaerobic bacteria is not known**

58 Following the same path, little is still known about the antibiotic susceptibility patterns of
59 “anaerobic bacteria”. In clinical practice, the spectrum of an antibiotic refers to the array of
60 bacteria against which it is active at non-toxic dosing. Accordingly, an antibiotic is considered
61 active on one species if it achieves concentrations above the minimal inhibitory
62 concentrations (MICs) of wild-type strains at various body sites. Whereas easily culturable
63 anaerobic bacteria such as *Bacteroides* spp. and *Prevotella* spp. have been widely studied,
64 the susceptibility profiles of the vast majority of “anaerobic bacteria” remain unreported to
65 date. A quantitative dimension of the lack of knowledge about antibiotic susceptibility can be
66 addressed by the analysis of the EUCAST2 repository (<https://mic.eucast.org/Eucast2/>). It
67 offers more than 20,000 MICs distributions (antibiotics/species) with ten genera from
68 anaerobic bacteria for which data are present in the literature: *Bacteroides*, *Bifidobacterium*,
69 *Clostridioides*, *Clostridium*, *Fusobacterium*, *Parabacteroides*, *Parvimonas*,
70 *Peptostreptococcus*, *Prevotella*, *Porphyromonas* (Table 1). Altogether, these genera make
71 61.8% of the overall bacterial abundance in the intestinal microbiota, but only 8.2% (10/122)
72 of all genera of anaerobic bacteria that could be observed (Li et al., 2014) (Figure 1). In
73 routine practice though, the antibiotic susceptibility patterns of anaerobic bacteria for which
74 no data are available are inferred by extension from the anaerobic bacteria for which data
75 are. Interestingly, functional metagenomic studies and *in silico* bioinformatic analyses have
76 demonstrated that “anaerobic bacteria” harbour a large panel of antibiotic resistance genes

77 (ARG), however distantly related to those deposited in public databases(Ruppe et al., 2019,
78 Sommer et al., 2009). Moreover, anaerobic bacteria can also exchange ARGs through
79 horizontal gene transfer and become resistant to some antibiotics by mutations in specific
80 genes(Veloo et al., 2019). Hence, we can assume a great diversity of antibiotic susceptibility
81 profiles in anaerobic bacteria, even within a single species, and that the antibiotic
82 susceptibility pattern of wild-type strains does not preclude the presence of acquired
83 resistance in clinical isolates. In all, the term “anti-anaerobic spectrum” is poorly supported by
84 the lack of knowledge about antibiotic susceptibility in anaerobic bacteria, and so does its
85 translation into the clinical practice.

86

87 **The impact of antibiotics on the intestinal microbiota is not linked with their supposed**
88 **“anti-anaerobic” spectrum**

89 Despite the current lack of knowledge on their antibiotic susceptibility patterns, using
90 antibiotics with an “anti-anaerobic” spectrum to target infections caused by anaerobic
91 bacteria is common routine (e.g., in patients with aspiration pneumonia, brain abscesses,
92 Fournier gangrene, or intra-abdominal infections). Because infections involving anaerobic
93 bacteria usually include multiple species(Brook, 2007), the majority of which are either not
94 detected or not accurately identified by standard procedures, these microorganisms are
95 commonly reported as “presence of anaerobic bacteria” by clinical laboratories, thereby
96 encouraging the use of antibiotics according to their supposed “anti-anaerobic” spectrum
97 such as beta-lactam/beta-lactamase inhibitor combinations, clindamycin, or metronidazole.
98 Moreover, some infections actually involve anaerobic bacteria while none is recovered by
99 culture. Indeed, culture-independent methods applied to clinical samples have showed that
100 anaerobic bacteria were frequently found aside conventional pathogens. This has been
101 recently illustrated by the capacity of shotgun metagenomics to detect anaerobes in
102 necrotizing soft-tissue infections(Rodriguez et al., 2020) or bone and joint infections(Ruppe
103 et al., 2017), while these bacteria were not necessarily suspected or targeted by the definite

104 antibiotic regimens as long as only the results of the standard culture were available.
105 Nonetheless, it is very likely that in infections involving multiple anaerobic bacteria, the
106 administered antibiotic treatment may not be active on each “anaerobic” bacterial species,
107 without this seems to have any negative impact on its success.

108

109 **The impact of antibiotics on intestinal microbiota is only poorly linked with their**
110 **supposed “anti-anaerobic” spectrum**

111 In order to cope with the current increase of multidrug resistant (MDR) bacteria, a careful use
112 of antibiotics is recommended(Timsit et al., 2019). In this purpose, antibiotic stewardship
113 aims at selecting molecules that combine an optimal clinical efficacy with the minimal impact
114 on intestinal microbiota, which constitutes the main reservoir for MDR bacteria (e.g.,
115 extended-spectrum β -lactamase-producing Enterobacterales, carbapenem-resistant
116 Enterobacterales or glycopeptide-resistant enterococci) and thereby the source for various
117 infections. However, very few data are available about the comparative impacts of antibiotics
118 on the intestinal microbiota. Studies on mice clearly demonstrate that so-called “anti-
119 anaerobic” antibiotics like piperacillin-tazobactam or clindamycin are strong drivers of
120 anaerobic microbiota disturbance and decrease in intestinal colonization resistance(Perez et
121 al., 2011). Such molecules have also been identified in humans as factors associated with
122 MDR bacteria acquisition in environments with substantial colonization pressure(Boutrot et
123 al., 2019). This association between MDR bacteria acquisition and exposure to alleged “anti-
124 anaerobic” molecules supports the recommendations of using a molecule devoid of “anti-
125 anaerobic” properties in a de-escalation perspective. This parameter is also regularly taken
126 into account in the ranking of beta-lactams or other antibiotics according to their impact on
127 intestinal microbiota(Weiss et al., 2015). However, emphasizing the “anti-anaerobic” trait of
128 antibiotics as a key-driver of harming the microbiota and promoting the acquisition of MDR
129 bacteria may be misleading. A seminal study aiming to assess the impact of ciprofloxacin on
130 the intestinal microbiota is from this point of view illustrative. Although ciprofloxacin is

131 considered to have limited activity in infections caused by anaerobic bacteria, it strongly
132 affects the composition of the intestinal microbiota when given to healthy
133 volunteers(Dethlefsen and Relman, 2011). Indeed, ciprofloxacin has a substantial biliary
134 excretion leading to very high intestinal concentrations that seem to exceed the putative
135 MICs of most anaerobic species residing in the gut. Another recent illustration of the risk of
136 acquisition of MDR bacteria has been showed with amoxicillin, which is generally not
137 considered as an “anti-anaerobic” antibiotic and thereby to have only a minimal impact on the
138 intestinal microbiota. In a study performed in children from Niger where the extended-
139 spectrum beta-lactamase – producing Enterobacterales (ESBL-E) carriage rate was ranging
140 around 30%, ESBL-E acquisition was compared in two groups: one treated with a 7-days
141 course of amoxicillin and the other with placebo. Interestingly, a significant difference was
142 observed between the two groups with ESBL-E acquisition rates being 54% in the amoxicillin
143 group and 32% in the placebo group (OR: 2.29 [1.41–3.69]). These findings suggested that
144 even antibiotics not considered to treat infections caused by anaerobic bacteria can affect
145 the intestinal microbiota in promoting the acquisition of ESBL-E by reducing the colonization
146 resistance in the bowel(Maataoui et al., 2020). Indeed, the impact of antibiotics in the gut is
147 barely predictable from their sole clinical spectrum, underlying again the weakness of the
148 concept of “anti-anaerobe” antibiotics in the field of ecological studies.

149

150 **Conclusion and perspectives**

151 In all, we assume that the current knowledge gaps still remain regarding anaerobic bacteria,
152 especially with respect to their susceptibility to antibiotics. Accordingly, the concept of “anti-
153 anaerobic” spectrum of antibiotics should be acknowledged as poorly supported.
154 Furthermore, the term “anti-anaerobic” does not guarantee that such an antibiotic would be
155 active on the anaerobic bacteria that can be involved in an infection, and it may even be
156 misleading when it comes to the impact of antibiotics on the gut microbiota. This situation
157 may change in the near future with the development of new generation sequencing (NGS)-

158 based tools in the field of microbiological diagnosis. By sequencing all the nucleic acids
159 extracted from clinical samples, these methods make possible to easily detect and identify all
160 microorganisms, including the anaerobes, as well as the associated resistance genes.
161 Although important progress regarding the correlation between genotypes and antibiotic
162 susceptibility phenotypes have been done in other bacteria like Enterobacterales (Ruppe et
163 al., 2020), the signification of the presence of resistance genes in anaerobes is still difficult to
164 interpret and further studies on that question are warranted. Finally, we hope that future
165 studies gathering NGS-based information and clinical efficacy of antibiotic protocols will help
166 to elaborate effective antibiotic schemes according to the species identified and the
167 resistance genes detected. Hence, pending for further insights on this issue, we propose to
168 use this term with extreme caution.

169

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175

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178

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224 **Table 1:** List of the genera of the anaerobic bacteria included in the EUCAST2 minimal
 225 inhibitory concentrations (MICs) distribution and their relative abundance in the gut
 226 microbiota(Li et al., 2014).

227

Genus	Species	Data on EUCAST2	9.9M gene catalogue relative abundance (% , genus level)
<i>Bacteroides</i>	<i>caccae</i>	53	48.1
	<i>capillosus</i>	2	
	<i>fragilis</i>	21871	
	<i>ovatus</i>	875	
	<i>thetaiotaomicron</i>	3625	
	<i>uniformis</i>	249	
	<i>vulgatus</i>	798	
	spp	296	
<i>Bifidobacterium</i>	<i>longum</i>	517	1.4
	<i>pseudolongum</i>	246	
	<i>thermophilum</i>	240	
	spp	2122	
<i>Clostridioides</i> ^a	<i>difficile</i>	49379	NA ^b
<i>Clostridium</i>	<i>butyricum</i>	2	2.9
	<i>perfringens</i>	1043	
	<i>ramosum</i>	16	
	<i>septicum</i>	1	
	<i>sporogenes</i>	5	
	spp	1001	
<i>Fusobacterium</i>	spp	852	0.1
<i>Parabacteroides</i> ^c	<i>distasonis</i>	421	1.8
<i>Parvimonas</i> ^d	<i>micra</i>	111	NA ^b
<i>Peptostreptococcus</i>	spp	1054	0.01
<i>Prevotella</i>	spp	2260	7.5
<i>Porphyromonas</i>	spp	152	0.03

228

229 ^aThe numbers from *Clostridium difficile* were considered.

230 ^bThe genera *Clostridioides* and *Parvimonas* were absent from the gene catalogue.

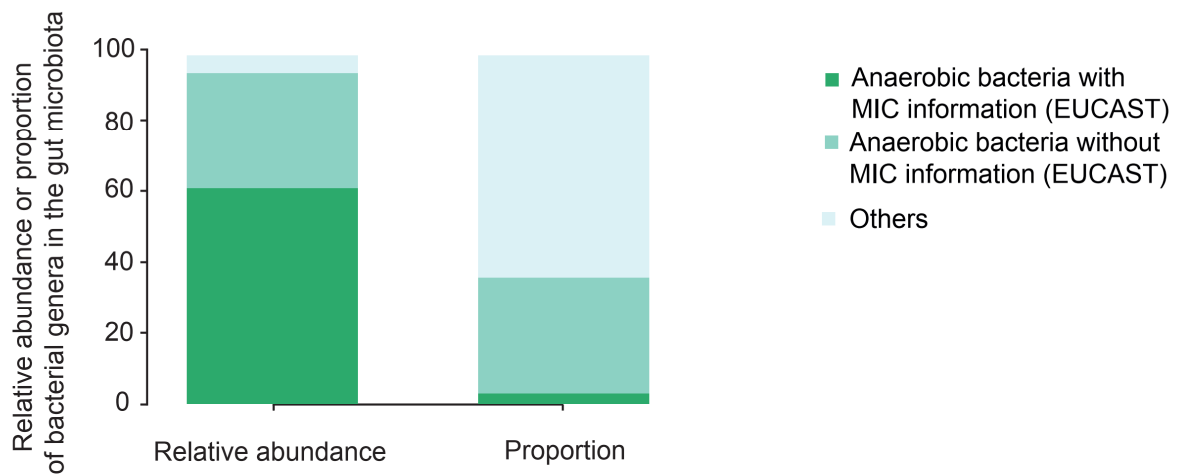
231 ^cThe numbers from *Bacteroides distasonis* were considered.

232 ^dThe numbers from *Peptostreptococcus micros* were considered.

233

234 **Figure 1:** Bacterial genera present in the intestinal microbiota according to their (i) growth
235 atmosphere: anaerobic bacteria and others (non-strict anaerobic bacteria) and (ii) the
236 availability of antibiotic susceptibility data in the EUCAST2 repository (for anaerobic
237 bacteria). The bar on the left depicts the relative abundance of the genera while the bar on
238 the right depicts the proportion of the genera in a 9.9 million genes catalogue build from the
239 metagenomic sequencing of faecal samples passed by 1,267 individuals³.

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