DYSBIOSIS OF THE GUT MICROBIOTA

Multiple clinical consequences

Disorders associated with imbalances of the gut microbiota caused by antibiotics intake or gastrointestinal infections

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Editorial

Gut microbiota and dysbiosis: what are we talking about?

Dr ALEXIS MOSCA

Robert-Debré Hospital, Paris
UMR1149 "Intestinal Inflammation"
Inserm and Université Paris Diderot,
Faculté Xavier-Bichat, France.

The gut microbiota consists of around 10^{13} bacteria, which is about the same as the number of eukaryotic cells in the body[1]. It is a stable ecosystem living in symbiosis with the host individual. The gastrointestinal tract of every adult harbors 500 to 1,000 different bacterial species. In humans, there is a core set of species that are both dominant and prevalent[2]. Its composition is influenced by many intrinsic and environmental factors.

The gut microbiota plays an essential role in several physiological processes. It limits the growth of pathogenic microorganisms by competing for nutrients, by providing a barrier effect or by producing bactericidal substances. Beyond the intestinal mucosa, the microbiota helps to maintain a functional immune system. It also has a housekeeping role by renewing the intestinal epithelium and it also plays a role in metabolism through the production of vitamins (vitamin K for example) and the transformation of complex sugars.

The equilibrium of the gut microbiota can however be durably "disrupted". A number of factors come into play, including **intestinal infections** (viral, bacterial, parasitic), drugs (**antibiotics in particular**), changes in diet, stress, to name a few.

What follows is a **reduction in bacterial diversity** and a weakened resistance to pathogenic microbes like toxinogenic *Clostridioides difficile* (*C. difficile*, formely *Clostridium difficile*). **Dysbiosis can be thought of as a rupture of the symbiosis between the microbiota and the host.** But by the way, what is dysbiosis? Can we today define a «healthy» microbiota as we would define a normal blood ionogram? Can we say by analyzing the bacteria that populate our intestines if our microbiotic organ is doing well like a heart whose ventricular ejection fraction would be evaluated on ultrasound? The answer today is «no» and we have some clues that it will remain negative. Two recently published studies confirm this.

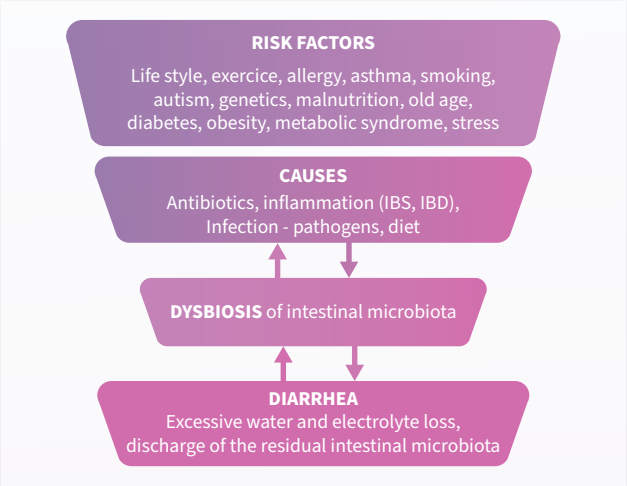


Figure 1. Dysbiosis risk factors and causes during diarrhea. Adapted from MoréMI & Swidsinski A. *Clin Exp Gastroenterol.* 2015;8:237-255; Levy *et al. Nat Rev Immunol.* 2017;17(4):219-232; Ortiz-Alvarez *et al. Clin Transl Gastroenterol.* 2020 Feb; 11(2): e00126; Robless *et al. Br J Nutr.* 2013;109 Suppl 2:S21-S26; Iebba *et al. New Microbiol.* 2016;39(1):1-12.

In the first study, the intestinal microbiota of more than 7000 individuals (these are Chinese living in the same province but in 14 different districts) was analyzed[3]. As expected, each individual had his/her own intestinal bacterial composition. But what factor did vary the most about this composition? Quite simply his/her place of residence, much more than his/her food, or his/her way of life. More specifically now, let's look within the same district, if the microbiota of people with type 2 diabetes (T2D) is different from those who don't have it. Yes, indeed, by analyzing the microbiota of individuals in this district, we can separate T2D individuals or not with a probability of around 75%. But if we apply this method to individuals living in the district next door, the prediction drops to 50%, as much as to say that we no longer predict anything. This means that the «dysbiosis» associated with T2D identified in one district is not the same in the next district. Imagine then wanting to describe a «universal» dysbiosis for all individuals from different regions and countries.

In the second study, the microbiota of 2 individuals (A and B) was analyzed daily for one year[4]. For A., the microbiota is stable for months and then changes radically during a trip abroad, returning a few days later to its previous state. He, therefore, had an «acute» dysbiosis which his microbiota - resilient - corrected on his own. For B., we see that his microbiota also remains sandy for months and then changes greatly during an infectious episode and then returns to a stable state but different from its previous state. This time, the infection-induced dysbiosis was not corrected identically but led to another stable composition of the gut microbiota. Can we speak of «chronic» dysbiosis? In fact, everything depends on the health of B. If he is in good health, it will be said that he has a 'normobiosis' different from the previous one. But, if, on the other hand, he develops a post-infectious irritable bowel syndrome, for example, we can talk about 'chronic' dysbiosis that we can try to correct with modifiers of intestinal flora such as pre- or pro-biotics.

We, therefore, see in the light of the analysis of these 2 examples taken from recent publications that **« dysbiosis » is not universal and is defined for each individual, according to their state of health.**

Contents

In this document, we will focus on the clinical consequences following dysbiosis induced by antibiotics and intestinal infection only. Other causes of dysbiosis are sometimes well characterized but clinical consequences are less obvious.

Dysbiosis in infants and children: clinical consequences

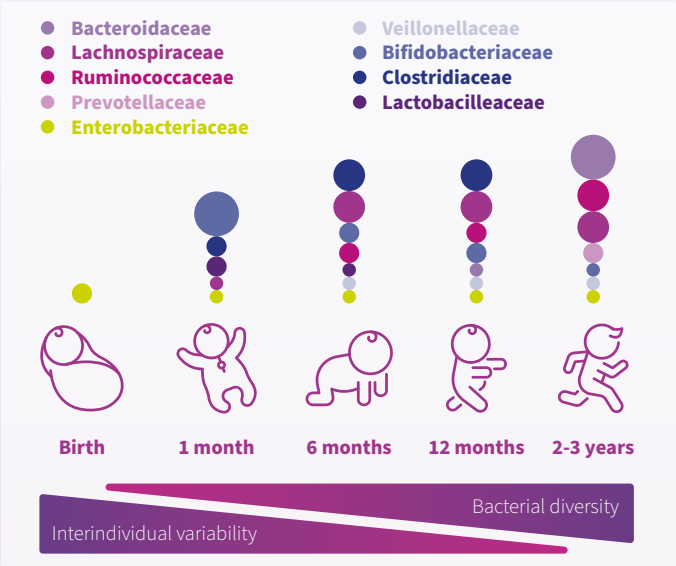


Figure 2. Stages of microbial colonization of the infant and child intestine. Adapted from Arrieta *et al. Front Immunol.* 2014; 5: 427.

Common factors inducing a dysbiosis in children are **infectious diarrhea** and **antibiotic treatment.** One the one hand, infectious diarrhea causes **abrupt changes in the gut ecosystem,** affecting its abiotic conditions (rapid transit, looser stools, etc.) and the gut microbiota by introducing one or more pathogens[5] as bacterial, viral and parasitic organisms[6]. **In acute diarrhea,** there is a loss of the barrier effect and a reduction in the diversity of gut bacteria[7,8]. **Diarrhea is usually a warning signal of a disturbance in the gut ecosystem**[6]. To treat acute diarrhea, WHO recommends rehydration with oral rehydration salts solution. Probiotics, as adjuvant therapies, have also been recommended[9] to prevent and treat acute diarrhea.

On the other hand, antibiotics have been saving many lives over the past century and are a common prescription for children in westernized countries[10]. Beside their role in eradicating a specific infection, they also will disrupt the intestinal microbial ecosystem. Even in a healthy adult, we do know that the **recovery** of the previous bacterial composition could be only **partial up to 6 months after an antibiotic course**[11]. The resilience of the ecosystem is mostly due to the gut microbiota basal composition of the individual[12], highlighting the **importance of shaping a healthy microbiome from birth.** The time of the perturbation is also very important: an antibiotic-induced disruption of the gut microbiota early in life – when the microbiota is still immature and unstable - might have **long term consequences on its composition later in life**[13]. For example, just a single dose of intrapartum antibiotic prophylaxis to the mother may have consequences on the gut microbiota composition of the offspring up to the age of 1 year[14]. In the same way, a single antibiotic course in early life disrupts the gut microbiota composition up to 3 months later[15]. Therefore, it is not surprising that antibiotic-induced **dysbiosis in infants and children may have short-term but also long-term clinical consequences**[16].

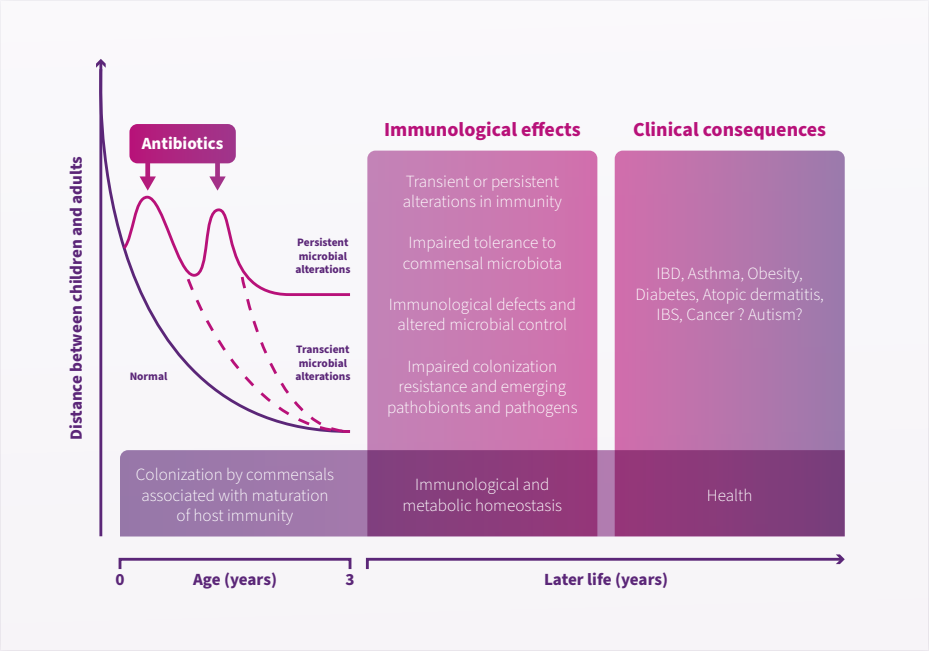


Figure 3. Microbial colonization, development of the immune system and their perturbation by treatment with antibiotics early in life. Microbial colonization during early postnatal development represents a dynamic process, which evolves toward an adult-like configuration within 3 years after birth. Adapted from Zeissig *et al. Nat Immunol.* 2014;15(4):307-310.

Next subchapters will present dysbiosis triggered in childhood and potential clinical consequences for health.

Antibiotic-Associated Diarrhea (AAD)

Antibiotic-associated diarrhea is defined as diarrhea which occurs in conjunction with antibiotics administration[17]. AAD has been recognized as a clinical concern since the 1950s, when antibiotic use increased significantly. Prevalence of AAD can differ with antibiotic prescribed and extreme age of life (elderly or young children). Its mean duration is 7 days[18].

Treatment for uncomplicated cases of AAD is to discontinue or change the antibiotic if possible. For more serious cases of AAD (as *C. difficile* disease) other treatments are needed like specific antibiotic, probiotic therapy, fecal microbiota transplant[18].

In a study conducted over an 11-month period in 650 children aged 1 month to 15 years treated with antibiotics for an infection, 11% had an episode of diarrhea. The **incidence of AAD was especially high after the administration of certain antibiotics** (amoxicillin alone or in combination: **+ 23 %;** p = 0.003 compared with other antibiotics[19] (Figure 4).

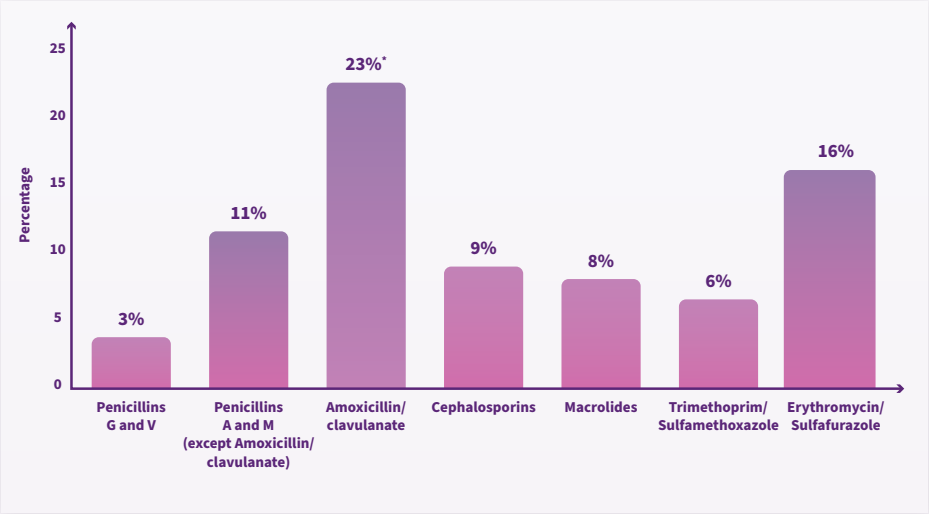


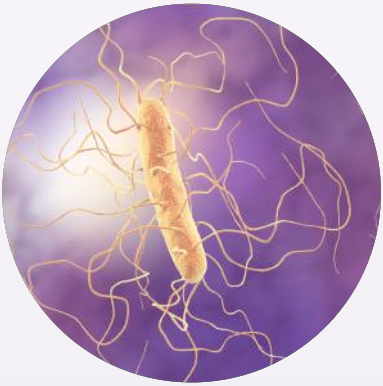
Figure 4. Indidence of episodes of diarrhea according to antibiotics prescribed versus all other antibiotics taken together *p=0,003. Adapted from Turck *et al. J Pediatr Gastroenterol Nutr.* 2003;37(1):22-26.

Early antibiotic exposure in infants is associated with an increased rate of diarrhea during childhood. Exclusive breastfeeding during the first six months of life may have a protective effect[20]. As antibiotic exposure in children can lead to AAD, simultaneous use of a probiotic not sensitive to antibiotic may be an effective prophylactic strategy[18].

Dysbiosis in adults: clinical consequences

Next subchapters will present dysbiosis triggered in adult and potential clinical consequences for health.

Antibiotic-Associated Diarrhea (AAD) and *C. difficile* disease



AAD is a major side effect of antibiotic treatment in children but also in adults. **Antibiotic treatment disturbs the gut microbiota, leading to dysbiosis and can lead to diarrhea.** Commonly used antibiotics lead to a 25% reduction in microbial diversity[53] and **up to 35% of patients taking antibiotics will experience antibiotic-associated diarrhea**[18]. Persistence of gut microbiota alterations (sometimes up to 3 months) may explain susceptibilities to AAD. The **reduced diversity of gut microbiota can subsequently allow the growth of pathogens** such as *C. difficile* (almost one-third of AAD cases), *Clostridium perfringens*, *Staphylococcus aureus* and other pathogens[54].

C. difficile is a gram-positive, spore-forming anaerobic bacillus that can be associated with gastrointestinal manifestation from uncomplicated diarrhea, to nonspecific colitis or pseudomembranous colitis[55]. *C. difficile* toxins can be found in the stool of 15% to 25% of patients with AAD[55] and is the most commonly reported pathogen in hospitals[56]. **Recurrence is one of the most challenging complications of *C. difficile*-associated disease (CDAD)** with 12% to 24% of patients developing a second episode of CDAD within 2 months of the initial diagnosis[55].

These findings suggest that **strategies to reinforce the ability of the gut microbiota to resist and prevent modifications caused by antibiotics would be of major clinical interest.**

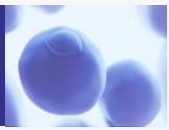
The role of probiotics in gut microbiota balance*

*** This part must be adapted to your local regulatory constraints (drug, food supplement or medical device status)**

Gut microbiota is a stable ecosystem in symbiosis with the host and is sometimes referred to as an organ itself. Homeostasis of gut microbiota plays an important role in host health.

As described previously, perturbation of this homeostasis by antibiotics or intestinal infection can lead to dysbiosis and subsequently further disorders. Strategies to modulate gut microbiota include probiotics, aiming at restoring a balance.

***Saccharomyces boulardii* CNCM I-745**



As an example, *S. boulardii* CNCM I-745 is a probiotic that holds several marketing authorizations around the world, has clinically demonstrated efficacy **to prevent antibiotic-associated diarrhea (AAD) to prevent diarrhea in children and adults**

Several studies provided evidence of *S. boulardii* CNCM I-745 efficacy in preventing antibiotic-associated diarrhea, recurrence of *C. di icile* disease (CDD) combined with standard antibiotics and digestive side effects during *Helicobacter pylori* eradication therapy.

Prevention of antibiotic-associated diarrhea

A meta-analysis performed by Szajewska *et al.* in 2015[70], using 21 randomized controlled trials with 4780 participants, **confirms that *S. boulardii* is effective in reducing the risk of antibiotic-associated diarrhea by 57% in children and by 51% in adults.**

In children treated with antibiotics[71], *S. boulardii* CNCM I-745 significantly reduces the prevalence of antibiotic-associated diarrhea by 78%. In adults treated with antibiotics[72], *S. boulardii* CNCM I-745 decreases antibiotic-associated diarrhea from 9% in placebo group to 1.4% in study group ($p<0.05$).

As *S. boulardii* is a yeast naturally non susceptible to antibiotics[73] it can be taken at the same time as antibiotics. Also, *S. boulardii* CNCM I-745 does not alter the efficacy and pharmacokinetic parameters of antibiotic (amoxicillin)[74]. Those results highlight the potential of *S. boulardii* CNCM I-745 to prevent diarrhea during antibiotic treatment without interfering with it.

International recommendations to prevent diarrhea in children and adults

Children

Disorders	Society	Recommendation
Antibiotic-associated diarrhea	European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[79]	*S. boulardii* and LGG are probiotics recommended to prevent AAD
	World Gastroenterology Organisation[9]	
	Recommendations for the management of gastrointestinal disorders in children in the Asia-Pacific region[80]	
	Latin-American Experts Consensus Group for the use of probiotics in paediatric Gastroenterology[81]	
	Groupe Francophone of Hepathology-Gastroenterology and Pediatric Nutrition[89]	

Adults

Antibiotic-associated diarrhea	World Gastroenterology Organisation[9]	*S. boulardii* CNCM I-745 is one of the probiotics recommended to prevent AAD in various clinical settings

Tableau 1. International recommendations for the use of *Saccharomyces boulardii* CNCM I-745 and other probiotics to prevent diarrhea.

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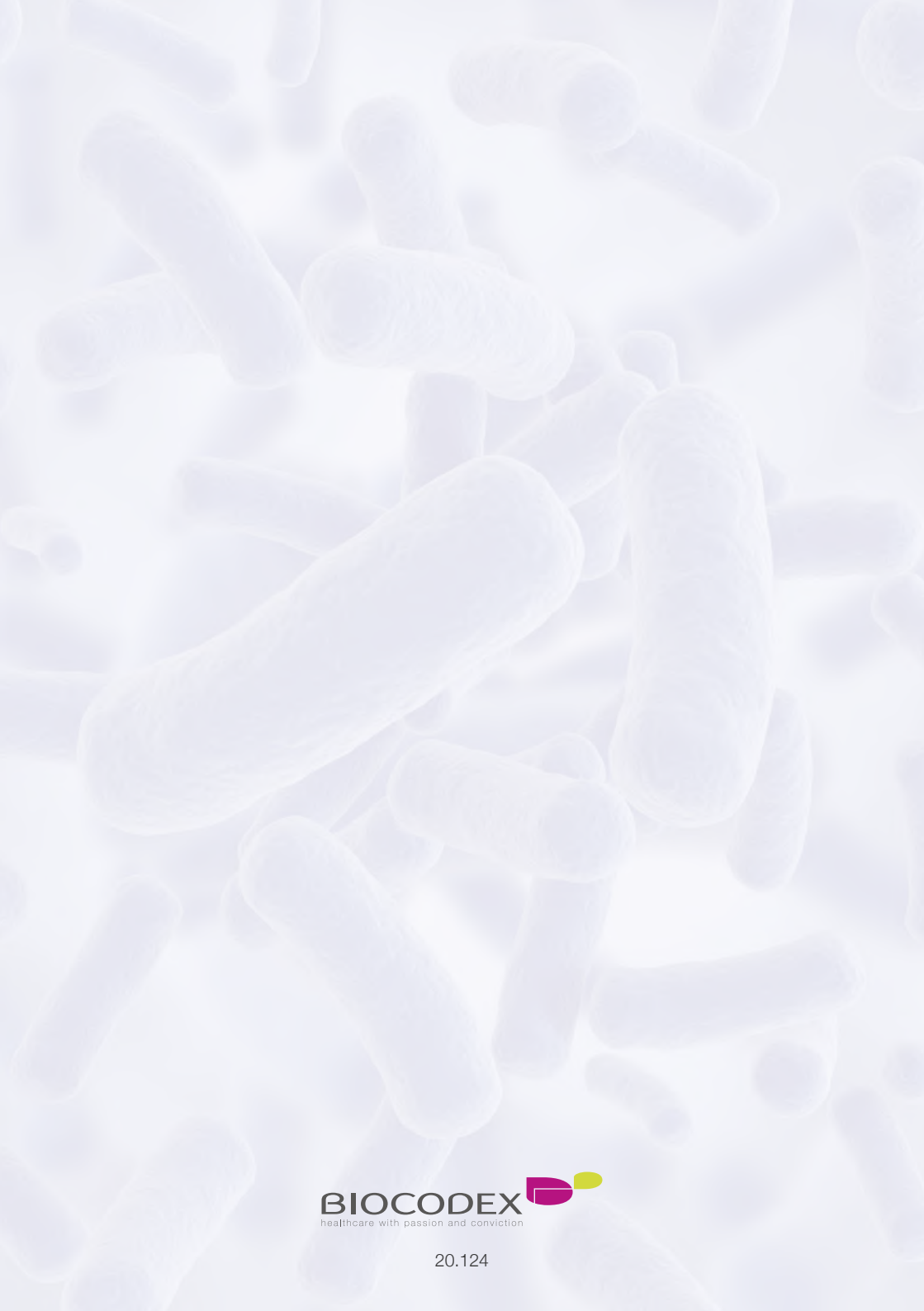
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